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JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 21 1961

TRIAL OF LIVING ATTENUATED POLIOVIRUS VACCINE

A REPORT OF THE PUBLIC HEALTH LABORATORY SERVICE TO THE POLIOMYELITIS VACCINES COMMITTEE OF THE MEDICAL RESEARCH COUNCIL*

Plan of the Trial

The purpose of the investigation was to find out what system of dosage of Sabin vaccine would give the greatest degree of colonization of the gut and the best neutralizing antibody response when fed to infants who had not been given Salk vaccine and had not experienced natural infection with poliovirus. A total of 409 children were given the vaccine by mouth and their virus excretion and serological response investigated.

The Vaccine.—The vaccine used was from three batches of poliovirus—type 1, type 2, and type 3—manufactured for Dr. Sabin by Messrs. Merck, Sharp and Dohme. It was titrated and distributed by the Medical Research Council's Biological Standards Laboratory, and was given according to the following schedules:

Group I: One dose of trivalent vaccine containing 1,000,000 T.C.D.50 of each of the three types of poliovirus.

Group II: Three doses of the trivalent vaccine with four-week intervals between the doses.

Group III: Three doses of monovalent vaccine each containing 1,000,000 T.C.D.50 of the appropriate type of virus with four-week intervals between the doses. Type 1 was fed first, followed by type 3, followed by type 2.

The method of feeding varied in the different centres, some using syrup or milk as a vehicle, others delivering the vaccine straight into the baby's mouth with a syringe or pipette.

The Children.—The trial was confined to infants aged 6–12 months. To minimize the spread of vaccine virus in the community and to reduce the possibility of natural infection with "wild" enteroviruses most of these infants were from single-child families. They were divided into three groups on the basis of their day of birth. The families were visited twice weekly until one month after the last dose of vaccine, and any illness in the vaccinated child or the rest of the family was noted.

*The information was collated and analysed by Dr. A. J. H. Tomlinson and Dr. Joan Davies (County Hall). Those taking part in the investigation included Dr. B. R. Sandiford (Birmingham), Dr. H. G. M. Smith and Dr. G. I. Barrow (Bradford), Dr. J. E. Jameson (Brighton), Dr. H. R. Cayton and Dr. Suzanne Clarke (Bristol), Dr. D. G. Davies (Carlisle), Dr. W. Charles Cockburn, Dr. A. D. Macrae, and Dr. C. E. D. Taylor (Colindale), Dr. Pauline M. Poole and Dr. J. E. M. Whitehead (Coventry), Dr. B. Moore (Exeter), Dr. J. H. McCoy (Hull), Dr. G. B. Ludlam and Dr. B. P. Marmion (Leeds), Dr. N. S. Mair and Dr. Hélène Mair (Leicester), Dr. M. T. Parker and Dr. B. E. Andrews (Manchester), Dr. J. H. Hale and Dr. P. S. Gardner (Newcastle), Dr. E. R. Mitchell (Nottingham), Dr. E. H. Gillespie and Dr. Margaret Wilson (Sheffield), and Dr. M. H. Hughes (Winchester).

Laboratory Investigation

Seventeen laboratories took part in the study. Virus isolation was undertaken at 16 of them. Six titrated their own serum for neutralizing antibodies. Sera from the remaining 10 laboratories were examined at the Virus Reference Laboratory, Colindale. The strains used in the neutralization test were either the Sabin or other well-known laboratory strains. (For details see Table I.)

TABLE I.—*Distribution of the Vaccinated Infants According to Their Dosage Group and the Participating Laboratory*

Laboratory	Number of Infants					Serum Examined at
	Included in Analysis				Excluded from Analysis	
	Group I	Group II	Group III	Total		
Birmingham	5	8	2	15	2	Birmingham
Bradford ..	5	5	3	13	0	Colindale
Brighton ..	7	7	2	16	3	,,
Bristol ..	11	8	6	25	0	Bristol
Carlisle ..	16	8	2	26	0	Colindale
Colindale ..	1	1	3	5	2	,,
County Hall	14	11	11	36	5	,,
Coventry ..	4	0	1	5	2	,,
Exeter ..	9	6	6	21	0	,,
Hull ..	12	6	12	30	6	Newcastle
Leeds ..	7	4	10	21	2	Leeds
Leicester ..	10	2	5	17	8	Colindale
Manchester	12	13	9	34	17	,,
Newcastle	12	7	11	30	6	Newcastle
Nottingham	0	6	11	17	18	Nottingham
Sheffield ..	5	1	2	8	0	Sheffield
Winchester	4	11	6	21	0	Colindale
	134	104	102	340	69	

So far as was possible each infant was bled three times: before the vaccine was fed, one month after the last dose of vaccine, and finally six months after the last dose. Neutralizing antibodies to the three types of poliovirus were titrated by the cytopathic end-point method in the presence of 30–300 T.C.D.50 of virus.

Specimens of faeces were collected before the vaccine was fed and then twice a week until four weeks after the last dose. Some laboratories also examined specimens of faeces from the family of the vaccinated child. Secondary monkey-kidney cells were used for virus isolation. They were prepared from primary monkey-kidney monolayers distributed by the Biological Standards Laboratory following the method described by Mair and Tobin (1960). The exact technique of virus isolation was left to the choice of the individual laboratories, but always entailed the use of mixtures of type-specific neutralizing sera to separate the individual viruses when more than one type was present.

As might be expected, there was some variation in the results obtained by the different laboratories,

presumably owing to small differences in the serological and virus isolation techniques. This variation, which was never of sufficient magnitude to invalidate the general conclusions, is referred to later where it affects the interpretation of the detailed results.

Results

The distribution of infants between the different dosage groups and the different laboratories is shown in Table I. It will be observed that 69 children who were given the vaccine have been excluded from the analysis. The reasons for exclusion were as follows:

(*a*) *No serum examined after vaccination* (9 infants).

(*b*) *Insufficient specimens of faeces examined* (17 infants).—The original scheme called for seven or eight specimens of faeces after each dose of vaccine. Infants have been excluded when fewer than four specimens were examined in the four weeks after feeding vaccine.

(*c*) *Evidence of natural infection, past or present, with poliovirus* (9 infants).—This was defined as either isolation of poliovirus from an infant before vaccination, or the presence of antibody in high titre (>1/128) to a particular type in both the prevaccination and the six-month sera with no excretion of that type during the period of observation.

(*d*) *Vaccine given wrongly* (13 infants).—This was usually because one of the monovalent vaccines became "contaminated" with trivalent vaccine at the time of feeding.

(*e*) *Infants in group I from whom no six-month serum was examined* (21 infants).—It was found that the second serum from these infants, which was taken one month after their first and only dose of vaccine, often showed a poor antibody response, especially to types 1 and 3. In a number of these infants the third (six-month) serum revealed a good antibody response. In some infants the antibody detected in the second serum represented not a response to the vaccine but the persistence of maternal antibody.

Of the 340 infants included in the trial, 262 were 6–8 months old and 78 were 9–11 months. The proportion of younger and older infants was similar in the three groups, and in no group was there an excess of infants with maternal antibody.

Neutralizing Antibody Response

Table II shows the neutralizing antibody titres to the three types of poliovirus obtained in the three groups. All the sera in group I were from the third bleeding, but in groups II and III some sera were from the second bleeding—that is, were collected one month after the last dose of vaccine. The antibody titres of these second sera were similar to those of the third serum in the corresponding groups. All but two of the 35 children immunized at Nottingham were bled 11 to 14 months after their last dose of vaccine instead of at six months; it seemed best for the purpose of this analysis to exclude these results.

It will be seen that in group I nearly all the children responded to type 2 virus, but that about half failed to produce antibody to type 1 and type 3. In groups II and III most of the children responded to all three viruses. Most of those who responded to the vaccine produced antibody with a titre of 1/32 or more wherever their sera were titrated. The sera titrated at Colindale showed in general lower titres than those obtained elsewhere. It is therefore justifiable to discuss the antibody response in terms of mean titre only when the sera were examined in the same laboratory.

Table III shows the geometric mean titre of the sera examined at Colindale. It will be seen that in groups I and II given the trivalent vaccine the titre to type 2 virus was higher than that to types 1 and 3, but that in group III, in which type 1 virus was given first, the titre to type 1 was highest. The antibody response to type 1 was significantly better ($P<0.05$) in group III than in the other two groups. Although some of the other differences in titre in Table III may represent real differences in response, they are not significant at the 5% level.

TABLE III.—*Geometric Mean Antibody Titres on Sera from Third Bleeding Examined at Colindale*

Type	Group I. 82 Sera		Group II. 54 Sera		Group III. 39 Sera	
	No. of Infants Showing Response	G.M. Titre of Positive Sera*	No. of Infants Showing Response	G.M. Titre of Positive Sera*	No. of Infants Showing Response	G.M. Titre of Positive Sera*
1	41	1/71	52	1/88	39	1/222
2	80	1/194	54	1/186	38	1/81
3	35	1/79	53	1/43	36	1/34

* A positive serum was one with a titre of 1/8 or greater in a neutralization test.

In groups II and III the figures for infants showing a response differ from those given in Table II, which includes some sera taken at the second bleeding.

TABLE IV.—*Antibody Response in the Three Groups*

Type	Group I			Group II			Group III		
	No. Vaccinated	Showing Response*		No. Vaccinated	Showing Response		No. Vaccinated	Showing Response	
		No.	%		No.	%		No.	%
1	134	72	54	104	101	97	102	96	94
2	134	131	98	104	104	100	102	98	96
3	134	69	51	104	103	99	102	94	92

* A response to vaccine has been defined as a serum titre after vaccination of 1/8 or greater.

In Table IV the serological results are summarized to show the percentage of infants in each group who had a serological response to the vaccine defined as an antibody titre of 1/8 or more. In all three groups the response to type 2 was nearly complete, but, whereas

TABLE II.—*Titre of Neutralizing Antibodies After Vaccination in the Three Groups*

Type	Laboratory at which Serology Done	Group I. 134 Children					Group II. 104 Children					Group III. 102 Children				
		Final Serum Titre					Final Serum Titre					Final Serum Titre				
		<1/8	1/8	1/32	1/128 or More	Total	<1/8	1/8	1/32	1/128 or More	Total	<1/8	1/8	1/32	1/128 or More	Total
1	Colindale	41	7	20	14	82	2	11	26	25	64	2	0	7	39	48
	Other laboratories	21	3	5	23	52	1	0	12	27	40	4	1	5	44	54
2	Colindale	2	1	19	60	82	0	1	16	47	64	1	4	23	20	48
	Other laboratories	1	0	6	45	52	0	0	1	39	40	3	1	6	44	54
3	Colindale	47	4	14	17	82	1	19	31	13	64	5	11	25	7	48
	Other laboratories	18	0	7	27	52	0	1	9	30	40	3	1	13	37	54

Note.—All sera in group I were from the third bleeding, but 20 sera in group II and 18 sera in group III were from the second bleeding.

in group I only about half the infants responded to types 1 and 3, in groups II and III nearly all the infants did so.

Comparison of the antibody titres in the second and third sera from children in groups II and III showed that their response to the vaccine was well maintained over the five months between the two bleedings. Only in one instance was antibody present in the second serum but no longer detectable (at 1/8 dilution) in the third serum. The actual titres in the two sera are not strictly comparable, because the first and second sera were usually tested together, whereas the third serum was tested later. However, as is shown in Table V, the type 3 titres were apparently rather lower in the third serum than in the second. At Nottingham, where the third bleeding was made 11 to 14 months after the last dose, the results

TABLE V.—*Comparison of Antibody Titres in Second and Third Sera (Groups II and III)*

Type	Group	Ratio of Titre in 3rd Serum to 2nd Serum		
		Lower	Equal	Higher
1	II	13	46	23
	III	10	69	2
	Total	23	115	25
2	II	12	58	12
	III	12	58	11
	Total	24	116	23
3	II	35	40	7
	III	21	52	8
	Total	56	92	15

Both second and third sera examined from 82 children in group II and 81 children in group III.

obtained in groups II and III were substantially the same as those obtained one month after the last dose of vaccine on the same infants, and the same as those obtained in the six-month bleedings elsewhere.

Virus Excretion

The duration of excretion of the three types of virus by infants in the different groups is shown in Table VI. For the purposes of this analysis duration of excretion is taken as the interval from feeding the vaccine to the day on which virus was last isolated. The detailed results showed that in many infants virus was isolated from every specimen during the period of excretion. A certain amount of interference was observed between the three polioviruses given in the trivalent vaccine. The commonest manifestation of this was for type 3 virus to disappear for a time in the middle of the observation period—usually from about the 8th to 16th day—and then to reappear in the faeces in considerable amount. When a virus was detected in the faeces intermittently, it is reasonable to assume that it was in fact multiplying in the gut up to the time of its final isolation but that technical difficulties prevented its demonstration. The detection of small amounts of one type of poliovirus in the presence of large amounts of the other types demands the use of high-titre monospecific sera.

It is possible that some of the apparently discrepant results, where little or no virus excretion was demonstrated but a good serological response was obtained, were due to some degree of heterologous neutralization by the sera used in the virus isolation procedures. One laboratory experienced difficulty particularly in isolating type 2 virus. This may have been due to unsatisfactory conditions of collection and storage of the specimens, which came from a distance. Here a number of infants apparently never excreted type 2 virus but produced a satisfactory rise in antibody titre. In Table VII A, where duration of virus excretion is related to serological response, the results from this laboratory have been omitted and are presented separately in Table VII B.

It is shown in Table VII A that almost all the infants who excreted a virus for 14 days or more responded serologically to the virus. Most of those who excreted for six days or less had no serological response. It seems probable that in these infants the virus isolated had passed through the gut with the minimum of multiplication. The comparatively high proportion of infants in Table VII B who developed antibodies even when they had apparently been excreting virus for less than a week suggests that the isolation of virus from these infants was less satisfactory than from those in Table VII A.

The effect of virus excretion for more than six days but less than 14 days varied with the different virus types. With type 2 virus all the 17 infants in whom the last virus isolation occurred in the second week

TABLE VI.—*Duration of Virus Excretion*

Type	Group I. 134 Children					Group II. 104 Children					Group III. 102 Children				
	Not Demonstrable	Duration of Excretion (Days)				Not Demonstrable	*Duration of Excretion (Days)				Not Demonstrable	Duration of Excretion (Days)			
		1–6	7–13	14–20	21+		1–6	7–13	14–20	21+		1–6	7–13	14–20	21+
1	24	22	18	15	55	0	8	22	11	63	3	1	1	9	88
2	3	1	4	20	106	0	0	5	13	86	12	3	8	15	64
3	31	30	6	3	64	0	0	4	8	92	6	1	3	6	86

* Represents longest period of excretion after any one dose.

TABLE VII.—*Duration of Virus Excretion Related to Antibody Response (All Three Groups)*

A (Results from One Laboratory Excluded)

Type	Duration of Excretion (Days)	Final Antibody Titre		Total 310	% Sera with Antibodies
		<1/8	⩾1/8		
1	0–6	46	7	53	13
	7–13	12	25	37	68
	14+	3	217	220	99
2	0–6	5	6*	11	54
	7–13	0	17	17	100
	14+	1	281	282	100
3	0–6	63	1	64	2
	7–13	6	5	11	45
	14+	3	232	235	99

B (Results from the Laboratory Excluded from A)

Type	Duration of Excretion (Days)	Final Antibody Titre		Total 30	% Sera with Antibodies
		<1/8	⩾1/8		
1	0–6	2	3	5	60
	7–13	3	1	4	25
	14+	5	16	21	76
2	0–6	1	7	8	88
	7–13	0	0	0	—
	14+	0	22	22	100
3	0–6	2	2	4	50
	7–13	0	2	2	100
	14+	1	23	24	96

* Four of these children were examined at one laboratory, which had less than average success in isolating type 2 virus.

developed antibodies. With type 3 virus only 5 out of 11 such infants responded serologically; with type 1 the proportion was 25 out of 37.

Analysis of the results in infants who excreted type 1 virus for less than 14 days showed that more than 10 days' excretion was required to provide an adequate antigenic stimulus, but that two shorter periods of excretion were generally sufficient. For types 2 and 3 most children either excreted for at least 14 days or not at all, and therefore it is not possible to determine what was the minimum necessary duration of excretion. This seemed to be rather longer for type 3 than for type 2. For convenience, excretion of virus over a period long enough to provide an adequate stimulus is referred to as a virus "take." For type 1 this period is taken as 11 days' excretion or more, for type 2 7 days, and for Type 3 14 days.

Effect of Maternal Antibody

Infants taking part in the trial were bled before the vaccine was fed. It can be assumed that antibody present in this serum had either been passively transmitted from the mother or had arisen as the result of a natural infection after birth. Nine infants were excluded from the analysis for this latter cause. The number of infants with antibody to each of the three viruses at their first bleeding is shown in Table VIII, where it will be seen that about one-third of the younger infants had antibody but that this had largely disappeared in the infants aged 9 months and over. The proportion

TABLE VIII.—*Distribution of Pre-vaccination Antibody Titres*

Age of Infant	Antibody Titre to						No Pre-vaccination Serum
	Type 1		Type 2		Type 3		
	<1/8	⩾1/8	<1/8	⩾1/8	<1/8	⩾1/8	
6–8 months ..	154	95	173	76	172	77	13
9–11 ,, ..	68	4	64	8	67	5	6

of infants with initial antibody may appear to be unduly high until it is remembered that many of the mothers had been immunized with Salk type vaccine within the previous year.

The effect of this initial antibody on the response to the vaccine was different for the different groups. So far as type 2 was concerned maternal antibody had no demonstrable effect since, as was seen in Table II, nearly all the children responded to this type and those who did not had no maternal antibody. The same is true of types 1 and 3 in groups II and III. In group I, on the other hand, the presence of maternal antibody does seem to have had some effect. Thus, Table IX shows that, of those infants who had no detectable type 1 antibody in the initial serum, roughly two-thirds

TABLE IX.—*Effect of Maternal Antibody on Response to Type 1 and Type 3 Virus in Group I*

Type	Initial Antibody Titre	Total	Number with		Number with	
			Virus "Take"	No "Take"	Serological Response	No Response
1	<1/8	93	61 (66)	32	58 (62)	35
	⩾1/8	34	12 (35)	22	10 (29)	24
3	<1/8	104	51 (49)	53	51 (49)	53
	⩾1/8	23	12 (52)	11	12 (52)	11

Figures in parentheses represent percentages (seven infants had no pre-vaccination serum).

responded to the type 1 element in the vaccine whether virus excretion or the production of antibodies is taken as the criterion for a response. Of those infants with maternal antibody only about one-third excreted virus or responded serologically. This effect was peculiar to type 1.

It seems therefore that in group I the presence of maternal antibody adversely affected the chance of an infant responding to type 1 virus. However, the numbers were too small to give the difference a statistical significance. If attention is confined to the effect of maternal antibody on virus "take," the numbers may be increased by adding the 104 infants in group II (considering only virus excretion following their first dose of vaccine), and the 20 infants in group I who were excluded from the main analysis because no third serum was obtainable. The combined figures are summarized in Table X.

TABLE X.—*Effect of Maternal Antibody on "Take" of Type 1 and Type 3 Virus After One Dose of Trivalent Vaccine*

Type	Initial Antibody Titre	Total	Number with		% with Virus "Take"
			No Virus "Take"	Virus "Take"	
1	<1/8	166	69	97	58
	⩾1/8	79	47	32	41
	Total	245	116	129	53
3	<1/8	192	97	95	49
	⩾1/8	53	24	29	55
	Total	245	121	124	51

"Take" = { Excretion of type 1 virus for 11 days or longer. / 3 ,, ,, 14 ,, ,, ,, ,, }

Included: Groups I and II—225 (13 had no first serum). "Group I excluded from main analysis because no third serum was obtainable—20 (1 of the 21 infants mentioned under "reason (e)" had no pre-vaccination serum taken).

It will be seen that of those children who had no antibody to type 1 at the time of vaccination 58% had a satisfactory "take" when given one dose of trivalent vaccine, whereas only 41% of those who had antibody responded satisfactorily. The difference is of statistical significance ($P<0.01$). An almost identical result is obtained if a satisfactory virus "take" is defined as 7 or 14 days' excretion. The presence of antibody to type 3 virus was apparently without effect. That age was not responsible is shown by the fact that, of infants in group I who failed to respond, 25 out of 65 (38%) were under 9 months and 10 out of 28 (36%) over 9 months of age.

The probability is that maternal antibody can interfere with the antibody response to oral vaccine only when the antigenic stimulus is weak. This is borne out by the observations of Levine *et al.* (1961), to whose paper reference may be made for similar observations by previous workers.

Comparison of Different Dosage Schedules

Table XI shows the number of infants in the different groups that produced antibody to all three types of virus, to two types, to one type, and to none at all. It is apparent that the group I schedule (one dose of trivalent vaccine) was inadequate. The group II schedule (three doses of trivalent vaccine) gave rather better results than the group III schedule (three doses of monovalent vaccine) in that more infants responded to all three virus types. The difference in the proportion of triple responses between group II and group III remained

Table XI.—*Serological Response to the Three Dosage Schedules*

Serological Response	Group I	Group II	Group III
Triple	39 (29)	100 (96)	85 (83)
Double response (Missing type 1)	29	3	5
Double response (Missing type 2)	0	0	4
Double response (Missing type 3)	33	1	7
Single response (type 2)	30	0	1
No response	3*	0	0
Total	134	104	102

Figures in parentheses represent percentages.
* One infant excreted the virus for a short time.

essentially the same whether serological response, virus excretion, or a combination of the two was used to define a satisfactory response. On the other hand, the amount of type 1 antibody produced was higher in group III than in group II (Tables II and III).

It is of interest to note the effect of the third dose of trivalent vaccine in group II. This can be assessed by considering the number of infants who, up to the feeding of the third dose, had not experienced a "take" with a given type of virus, but who, after the third dose, did excrete that type for an adequate period. This may be regarded as a "useful" response to the third dose of vaccine. Out of the 104 infants in the group, 14 had a "useful" response from their third dose of vaccine to type 1 virus and three to type 3 virus. Without their third dose of trivalent vaccine these children would probably not have produced antibody to these viruses.

Doses of Vaccine That Had No Effect

Though the following figures are not evident from Table XI, it was observed that a small number of infants completely failed both to excrete virus and to produce antibody. In group I there were two such failures out of 134 doses fed. In group II one infant out of 104 failed to excrete any virus after the first dose of trivalent vaccine. None of these infants were excreting other detectable enteroviruses before the vaccine was fed. It is not, of course, possible to determine how many of the second and third doses of trivalent vaccine in group II "failed," since the susceptibility of the gut to poliovirus would have been altered by the first dose.

In group III three infants failed to excrete virus or respond to type 1, six failed with type 3, and four with type 2. Of those infants who failed with type 1, one was excreting an adenovirus before the vaccine was fed and vomited three times shortly afterwards. From another, Coxsackie B virus type 5 was isolated before and for three weeks after the type 1 vaccine. This infant also failed to excrete or respond to the type 3 vaccine. In another infant that failed to excrete type 3 virus, E.C.H.O. 9 virus was isolated twice from the stools during the four weeks after its second dose. Of the other five that failed with type 3 vaccine, three were given the vaccine at one centre on the same day and, although another infant was given the same virus on this occasion and responded, it seems probable that some local factor was responsible for these failures. There was no real suggestion of interference with the establishment of type 3 virus as a result of the continued presence of type 1 virus from the first feeding. Indeed, it was striking how suddenly and completely the new type replaced the old in those children who were still excreting type 1 when the type 3 vaccine was fed. Even those that failed to take with type 3 stopped excreting type 1 virus after receiving the type 3 vaccine. Four children in group III failed to excrete virus or respond to type 2 virus. Of these, three were fed at one centre (not the same as that mentioned above); and again it seems possible that some local factor, perhaps concerned with transport of the vaccine, was responsible.

One reason why fewer children in group III had a triple response to the vaccine when compared with group II was that if a dose of monovalent vaccine failed that child could not develop a response to that type. If a dose of trivalent vaccine failed the child had two other opportunities to respond.

Other Viruses.—Other viruses were isolated from time to time, but with the exceptions mentioned above—failure of type 1 and type 3 viruses in group III—did not appear to interfere with the establishment of the vaccine virus in the gut.

Effect of Vaccine on Health of Children

The infants and their parents were under close observation in that they were visited twice weekly for the collection of faeces specimens. No ill effects attributable to the vaccine were seen.

Infection of Household Contacts

Table XII sets out the numbers and proportions of household contacts that became infected with one or more types of poliovirus. These figures probably underestimate the proportion of household infections, since faeces were not examined regularly from every contact. Persons have been included in this Table even when only one specimen of faeces was examined from them during the time that the vaccinated infant was excreting poliovirus. Owing to the original plan of the trial, the number of children examined was small, but there is no doubt that the children were infected far more frequently than their parents.

Table XII.—*Infection of Home Contacts*

	Type 1		Type 2		Type 3	
	No. Exposed*	No. Infected	No. Exposed	No. Infected	No. Exposed	No. Infected
Children	16	5	15	9	10	5
Adults ..	153	3	176	23	147	7

* A contact is considered to have been "exposed" only when the vaccinated infant excreted virus, and when specimens of faeces from the contact were examined at the relevant time.
Infection per child exposures, 19/41 = 46%. Infection per adult exposures, 33/476 = 7%.

Other Investigations

During the course of the vaccine trial a number of minor investigations were carried out by individual laboratories.

Duration of Virus Excretion.—This was determined for a small number of infants in group 1. Virus was detected in the faeces for periods between 5 and 12 weeks after the dose of vaccine. The proportion of infants excreting virus four weeks after the single dose of vaccine in group I was much higher than the proportion excreting virus four weeks after the third dose of vaccine in groups II and III.

Amount of Virus in Faeces.—This was estimated in every specimen of faeces from 11 infants in the three

groups; appropriate neutralizing sera were added to replicate titrations so that each virus was estimated separately. After the first dose of vaccine, whether trivalent or monovalent, the amount of each type of virus that became established in the gut was usually 10^4 to 10^6 virus particles per gramme of faeces. Amounts of this order were still present four weeks after the first dose had been given. Four weeks after the third dose of vaccine the amount of virus in the stool was as a rule only 1/100 of this amount.

Re-feeding.—A single dose of trivalent vaccine was fed to 12 infants in group I six months after their original dose. Faeces were collected and examined as before. The results are given in Table XIII. It was observed that infants who had responded serologically to the original vaccine usually failed to show evidence of reinfection. Virus was recovered from all infants that had failed to respond originally, but the duration of excretion was shorter than would be expected from the results of the primary vaccination.

TABLE XIII.—*Effect of Re-feeding Vaccine*

		Serological Response to Original Vaccine	Virus Excretion after Re-feeding: Not at All	Virus Excretion after Re-feeding: One Occasion Only	Virus Excretion after Re-feeding: More than One Occasion	Re-fed
Group I	Type 1	+	6	1	1	Trivalent vaccine
		−	0	1	3	
	,, 2	+	11	1	0	,,
		−	0	0	0	
	,, 3	+	6	0	0	,,
		−	0	2	4	
	All types	+	23	2	1	,,
		−	0	3	7	
Group II	Type 1	+	4	5	2	Monovalent type 1
		−	0	0	0	

The results of feeding type 1 vaccine to 11 infants in group II at the time of their third bleeding, six are also given in Table XIII, were not quite so clear-months after the last dose of trivalent vaccine, which cut. All of these infants had responded by the production of antibodies to type 1 virus. This virus was isolated from seven infants after re-feeding—from five once, and from two on more than one occasion.

Discussion

The results of this investigation need little discussion. They show conclusively that, (*a*) judged by the neutralizing antibody response, infants of 6 months and over can be immunized satisfactorily by the oral vaccine provided that three doses of the trivalent or monovalent vaccine are given; (*b*) the antibody content of the blood was well maintained six months after the last dose of vaccine, and judged by the results from Nottingham the antibody levels were still satisfactory 12 months after vaccination; (*c*) antibody is produced only when the virus is able to establish itself in the gut and remain there for a sufficient length of time; and (*d*) the antibody content of the blood serum after the Sabin vaccine is of the same order as that after three doses of Salk vaccine.

In the two diseases that have been studied most—diphtheria and poliomyelitis—maternal antibody in the infant's circulation is known to interfere with the antibody response to antigen injected parenterally. This is understandable. On the other hand, there is no obvious reason why the antibody response to an antigen given by the mouth should be affected by the presence of maternal antibody. However, the figures recorded in Tables IX and X leave little doubt that the response to type 1 virus in infants having maternal antibody was less than in those without. This effect was observed only with type 1 virus and only in infants given the trivalent vaccine. Its explanation is doubtful. Without further evidence it would be premature to regard it as causal rather than as coincidental. It is a point of general interest and needs further study.

The number of infants that were re-fed with vaccine six months after the last dose was small, but their reaction was similar to that already recorded by Sabin. Briefly, those that had responded well to the original vaccine either could not be reinfected or, if they could, harboured the virus for only a short time. On the contrary, those that had failed to respond satisfactorily to the original vaccine were readily reinfected. Though the immunity of the gut develops alongside the production of antibody, it is presumably independent of it. It constitutes a valuable safeguard against infection with a virulent strain of poliovirus (Hale *et al.*, 1959), and, together with the neutralizing antibody, affords a double barrier against infection and disease.

The safety of the live vaccine is an important factor in any comparison between Sabin and Salk vaccines. So far as the vaccinated child is concerned the safety of the Sabin vaccine is not in any doubt. The virus excreted by some vaccinated subjects, which may infect their contacts, differs slightly from the original vaccine virus both in neurovirulence for monkeys and in certain *in vitro* characters (Sabin, 1959; Melnick, 1960; Dane *et al.*, 1961). Tests on a single *in vitro* character were carried out on virus excreted by a small number of infants in this trial. Strains of type 1 and type 2 virus were isolated which differed from the original vaccine strain in their ability to grow at 40° C. The changes in the virus do not appear to be progressive on repeated human passage (Smorodintsev *et al.*, 1959), and the relevance of these changes is discussed at length by Sabin (1959), who concluded that they were not significant in relation to the safety of the live poliovirus vaccine. Theoretically, of course, one of the viruses might regain full virulence; but in spite of the enormous scale on which the vaccine has been used no evidence has been forthcoming to show that this happens in practice.

Therefore, in comparing the value of the Salk inactivated vaccine injected parenterally and the Sabin living attenuated vaccine given by the mouth the factor of safety may be neglected. Experience has shown that three or four doses of Salk vaccine confer a high degree of protection from clinical disease in the individual, but do not ensure the immunity of the herd. The large outbreaks of poliomyelitis in the United States and Canada in 1959 occurred in countries in which vaccination had been in progress for four years. To ensure herd immunity the proportion of the susceptible population to be vaccinated and revaccinated might have to be increased to 80 or 90% or even higher. In some circumscribed populations this might be possible, but, bearing in mind that in western countries the

susceptible population includes numerous adults, and that there is no simple way of distinguishing between the susceptible and the resistant members, it would be unrealistic to imagine that, let us say, 90% of the entire population under 50 years of age could be vaccinated with three doses of the Salk product and preferably revaccinated, for some time at least, at yearly intervals.

The use of the Sabin vaccine removes this difficulty. The Russian method of giving it in sweets to children and adults makes it both simple and practicable to vaccinate virtually the entire population, and to revaccinate it if this is found to be necessary. The fact that it confers a gut immunity, which the Salk vaccine does not, is an added point in its favour; and its administration by the oral route cuts down the number of injections that infants and children have to suffer, and is therefore likely to interfere less with the general programme of immunization against whooping-cough, diphtheria, tetanus, and smallpox.

The present investigation has shown that three doses of trivalent vaccine, or three doses of monovalent vaccine given in the order type 1, type 3, and type 2, stimulate good antibody production in a high proportion of infants. The choice between the two schedules of dosage is a little difficult to make. The advantage of the monovalent series is that the response to type 1 virus is particularly good (Table III). The advantage of the trivalent series is that if, for some reason or other, an infant fails to respond to one type at the first feeding, it has two more chances, at the second and third feedings, whereas in the monovalent series it has no such chance. Perhaps the optimum schedule would be type 1, followed by types 2 and 3 together, followed by the trivalent vaccine. This would, however, prove too complicated. In practice, therefore, we would recommend the administration of three doses of trivalent vaccine, followed by one dose a year later. The use of the trivalent product means that only one vaccine instead of three separate ones would be necessary, thus adding to the simplicity of the procedure.

Summary and Conclusions

Infants of 6–12 months of age were given by mouth the living attenuated poliovaccine of Sabin according to three different schedules of dosage. Group I received a single dose of trivalent vaccine; group II three doses of trivalent vaccine at four-week intervals; and group III three doses of monovalent vaccine at four-week intervals in the order type 1, type 3, and type 2. Each dose of each type of virus contained 1,000,000 tissue culture doses (T.C.D. 50).

The investigation was carried out by 17 different public health laboratories in England during 1960, each laboratory using all three schedules. The infants were bled immediately before their first dose of vaccine, and again four weeks and six months after the last dose; their serum was titrated for neutralizing antibody to the three types of virus. After each dose of vaccine the faeces were cultured twice a week for four weeks for poliovirus. Analysis of the results was based on 134 infants in group I, 104 in group II, and 102 in group III (Table I).

The antibody response to type 2 virus was excellent in all three groups, but in group I only about half the infants responded to types 1 and 3. The best result was in group II, in which the proportions responding to types 1, 2, and 3 were 97%, 100%, and 99% (Tables II, III, IV, and V).

Colonization of the gut was again best with type 2 virus, and again best on the whole with group II, though the best response of all to type 1 virus, judged both by antibody production and by colonization of the gut, was in group III, in which type 1 vaccine was given by itself first of all. The difference, however, between groups II and III in this respect was small (Table VI). In all three groups the antibody response was seldom satisfactory unless the virus was demonstrable in the gut for a week or more some time after vaccination (Table VII).

In infants fed with the trivalent vaccine the presence of maternal antibody in the circulation appeared to interfere somewhat with the response to type 1 virus. This effect, the explanation of which is discussed, was not seen with the other two types or with the monovalent vaccine (Tables IX and X).

The few observations made on the spread of the virus among home contacts showed that children were very much more readily infected than adults (Table XII).

A few of the infants were re-fed with trivalent or monovalent vaccine six months after their last dose. In general, the virus failed to establish itself in the gut of infants that had given a good antibody response to the original vaccine, whereas in those that had not responded satisfactorily colonization of the gut occurred uniformly (Table XIII).

These results are discussed, and from them, and from the experience in Soviet Russia and in Czechoslovakia, the conclusion is reached that, in order to ensure immunity of the herd as well as of the individual to poliomyelitis, the Sabin vaccine is preferable to the Salk vaccine. Not only does it stimulate the production of antibody equally well, but it affords the additional safeguard of rendering the gut resistant to the implantation of the so-called wild poliovirus. Moreover, the use of the Sabin vaccine avoids the necessity of injections which interfere with the general immunization programme of the child against other diseases.

It is recommended that for the sake of simplicity and ease of administration the Sabin vaccine should be given in three doses of the trivalent mixture at four- to six-weekly intervals. Infants have to be fed by spoon or dropper, but for children and adults the Russian method of dispensing the vaccine in the form of sweets seems to be the method of choice.

This investigation could not have been carried through without the help of medical officers of health, paediatricians, general practitioners, health visitors, and others too numerous to name. To all of these the Public Health Laboratory Service is extremely grateful. We would express our thanks particularly to the Council of the Society of Medical Officers of Health for supporting it in the first place, and to the following medical officers of health and paediatricians who took part in its local organization and execution: Dr. H. O. M. Bryant (West Bromwich), Dr. R. J. Dodds (Smethwick), Dr. Jean E. Preston (Sutton Coldfield), Dr. R. M. Ross (Dudley), Dr. John Douglas (Bradford), Dr. W. S. Parker and Dr. A. M. Nelson (Brighton), Professor R. C. Wofinden and Dr. J. F. Skone (Bristol), Dr. James L. Rennie (Carlisle), Dr. T. M. Clayton (Coventry), Dr. E. D. Irvine (Exeter), Dr. Alexander Hutchison (Kingston-upon-

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CONTROL OF A STAPHYLOCOCCAL EPIDEMIC UNDER ADVERSE CONDITIONS

BY

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Inadequacies of staff, equipment, and premises can easily induce pessimism when one has to attempt the control of staphylococcal epidemics in many of our smaller hospitals. In the circumstances reported here all of these factors were present, and unusual difficulties were added by the nature of the patients—mentally subnormal but mostly active male children between the ages of 6 and 15 years. Our success in bringing an epidemic of cutaneous infections, due to *Staphylococcus pyogenes* (phage types 80 and 3B/3C+), rapidly under control was as unexpected as it was gratifying, and we present this account of our experience as an encouragement to others.

Description of Children's Unit Involved

(The following details were correct during the rise and fall of the epidemic. Some improvements have since been made.)

The unit is part of an upgraded Poor-Law institution of 297 beds, which caters for cases of mental subnormality, chronic sick, and geriatric "Part 3" cases (Kent County Council); and receives on licence chronic cases of mental disorder from a local mental hospital.

The children's unit is a modern brick building, 40 yards (36 m.) from the nearest other hospital block. It was originally built as a nurses' home, but was never used as such. It has two stories, with adequate window lighting; each window opens only to a 4 in. (10 cm.) gap top and bottom.

Ground Floor.—(*a*) The dining-room, 18 by 16 ft. (5.5 by 5 m.), contains three wooden tables with low padded tubular-metal chairs, and two old wooden tray chairs. (*b*) The kitchen has one gas stove, no refrigerator, poor washing-up facilities, and no tiles. All food is brought to this kitchen from the main hospital kitchen in metal containers on a wooden trolley. (*c*) The sister's office, 12 by 12 ft. (3.6 by 3.6 m.), has a desk, two chairs, and drug-and-instrument cupboard. Doctors' consultations and treatments are carried out here as there is no other more suitable room. (*d*) Potting-room, 13 by 8 ft. (4 by 2.4 m.), has one hand-basin, which is used by doctor and other staff. (*e*) Sluice-room, 9 by 6 ft. (3 by 2 m.), contains four low W.C.s and one hand-basin. (*f*) The bathroom has one bath, used for six spastic children. (*g*) The ground-floor dormitory, 18 by 14 ft. (5.5 by 4.3 m.), has six cot beds spaced 18 in. (4.6 cm.) apart. (*h*) The play-room, 18 by 14 ft. (5.5 by 4.3 m.), has no furniture. All floors are linoleum-covered.

Upper Floor.—This has (*a*) four dormitories—three 18 by 14 ft. (5.5 by 4.3 m.); and one 33 by 14 ft. (10 by 4.3 m.) with 26 beds in all; (*b*) two bathrooms, each with single bath and hand-basin; (*c*) one lavatory with three low W.C.s; (*d*) linen and clothes cupboards.

Outside is a cement playground 60 by 40 ft. (18 by 12 m.) surrounded by a high fence and a privet hedge.

The Patients.—All are male children between the ages of 6 and 15 years, all but six being between 7 and 10. The total numbers vary between 27 and 30. All are cases of severe mental subnormality: many are unable to talk or to feed themselves. Some are very destructive and dirty in their habits. At the time of the epidemic 22 were incontinent of urine and faeces; six were bed-ridden.

Staff.—There are a sister (a registered mental nurse), and five mental nursing assistants (including the night nurse). A night superintendent (a registered mental nurse) is on duty also for the whole hospital.

Development of Staphylococcal Sepsis

During 1958 the health of the children was good. During 1959 cutaneous infections gradually increased (see Chart): most of these were boils; a few cases of staphylococcal otitis externa and conjunctivitis occurred also.

The numbers of new independent lesions appearing in each month after April, 1959, were: May, 10; June, 14; July, 24; August, 27; September, 45; October, 49; November, 39 (up to November 15). During November boils appeared on the buttocks and limbs of one nurse and on the face and axilla of another.

Measures For Control

On November 11, 1959, one of us (V. H. B.) was called in consultation to suggest how the situation should be managed. It was obvious that there would be many difficulties in achieving what appeared to be the essential

conditions for gaining control. For example, there was nowhere to send patients who became free from lesions, and it was impossible to isolate them within the unit. Insufficient staff were available for barrier-nursing to be practised. Most of the children were active and ambulant, not easily kept apart, and they frequently removed their dressings. Chipped enamelled chamber-pots were used interchangeably for the children, who

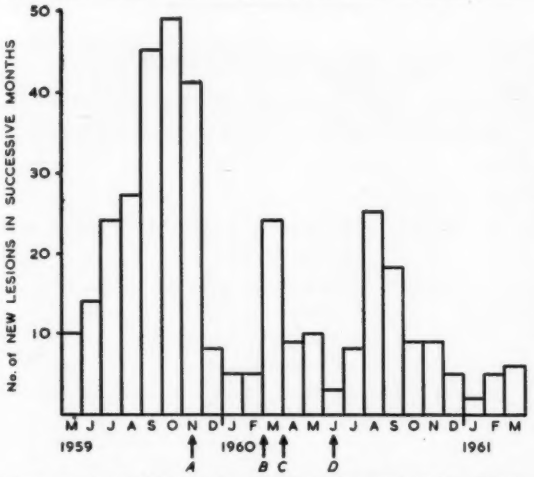

Chart of the Epidemic. A: Measures for control introduced, including naseptin cream for all patients and all staff, and hibitane sponging for all patients. B: Naseptin cream and hibitane sponging restricted to patients with lesions; suspended for other patients and for staff. C: Above procedures again extended to all patients, but not to staff. D: Naseptin cream again restricted to patients with lesions. Hibitane sponging retained for all patients.

sometimes exchanged pots in mid-session. In fact, many features of their day-to-day behaviour ensured that their bacterial flora would be shared between them.

At a conference between us and the sister-in-charge, the following measures were agreed to as practicable; and we wrote down individually what each of us had to do:

1. The noses of patients and staff would be swabbed weekly (one swab in both nostrils); and the discharges from all lesions would be swabbed also. Identification would be by labelling on the swab. No request forms would be required; and the sister was given permission to send swabs on her own initiative.

2. All the blankets (wool) in the unit, the mattresses, the pillows, and all articles of patients' clothing were initially to be autoclaved at 5 lb./sq. in. (350 g./sq. cm.) for 30 minutes. Subsequently woollen blankets would receive similar treatment whenever they were changed: as the woollen blankets deteriorated with this treatment they would be replaced by others of cellular cotton type which could be given high-temperature laundering.

3. All curtains were to be laundered, and the rooms were to be cleaned one at a time, using antiseptic for the walls and floors.

4. The enamelled chamber-pots were to be replaced by others of plastic material.

5. The baths, hand-basins, lavatory pans and seats, and chamber-pots were to be wiped over after use with "savlon" hospital concentrate 1 in 200.

6. Hibitane 1 in 5,000 was to be used in the bath-water.

7. Hexachlorophene ("cidal") soap was to be used for hand-washing, followed by hand-cream; and for bathing.

8. Antiseptic ointment was to be applied into both nostrils twice daily by all staff and all patients until directed otherwise. "Neobacrin" was used for about two weeks, after which "naseptin" cream was substituted.

9. The responsible authority was to be requested to provide more staff.

After consultation with Dr. J. Glover, consultant physician to the unit, it was decided to treat the boils by local measures only. The use of systemic antibiotics or sulphonamides was considered and rejected.

Active immunization, using staphylococcus toxoid or autogenous vaccine, was also considered, but we decided to keep this treatment in reserve until the results of our other measures were known. In the event we have had to do no more about it.

The measures agreed upon were all implemented within a few days of our conference. No additional staff were engaged, but a nursing assistant was sent from a near-by ward at intervals daily to assist with the extra duties.

[Proposals 2 and 6, above, were later modified in some particulars without reference to us, so that what actually happened was as follows: All the blankets, pillows, and mattresses (hair-stuffed) were autoclaved at 5 lb./sq. in. (350 g./sq. cm.) for 30 minutes, weekly from November, 1959, to March, 1960. After this the blankets were laundered with a quaternary ammonium compound, and in fact cotton cellular blankets have not been issued to the unit. The mattresses and pillows continued to be autoclaved weekly until September, 1960, then fortnightly until October, 1960, when new ones were supplied with plastic covers, which are wiped over weekly with savlon hospital concentrate 1 in 200. 1 in 5,000 hibitane in the bathwater was found to be too expensive, and it was replaced after a few weeks by the following procedure. Each patient was bathed in fresh clean water, using hexachlorophene soap. He was then sponged all over, including the hair, while standing in the bath, using a flannel soaked in 1 in 5,000 hibitane solution, which was contained in a bowl. A different flannel was used for each patient. Before and after use the flannels were mixed indiscriminately and stored in 1 in 200 savlon hospital concentrate. They were all boiled once daily.]

Results

Bacteriological

Staphylococci from all the boils which were present initially were submitted to Dr. R. O. E. Williams, who kindly determined their phage types. Six proved to be type 3B/3C+, and the other four type 80. All were resistant to penicillin but fully sensitive to streptomycin, chloramphenicol, chlortetracycline, and oxytetracycline.

Nasal swabs were not received until after intranasal antistaphylococcal cream had been applied for a week or more. Subsequently nasal swabs were received from patients at weekly intervals, with few exceptions, but from members of the staff very irregularly. Among the staphylococci from the noses of the staff the following phage types were identified by Dr. Williams: 80; 3B/3C+; 7/4E; 47/53 v.w.; 29/52; 73+.

Considering only weeks in which nasal swabs were received from at least 29 patients, the percentages of swabs yielding *Staph. pvogenes* at various dates were:

28/11/59	13/32	(39%)	9/1/60	8/29	(28%)
5/12/59	9/29	(31%)	16/1/60	3/32	(9%)
12/12/59	8/29	(28%)	30/1/60	3/29	(10%)
19/12/59	9/32	(28%)	13/1/60	4/29	(14%)
26/12/59	9/33	(29%)	20/2/60	6/29	(21%)

All swabs were taken by the sister-in-charge.

No definite relationship was seen between the number and duration of the lesions in any particular patient and the total number of nasal swabs from him which yielded *Staph. pyogenes*. Moreover, lesions were frequently present when the nasal swab was negative, and vice versa. In fact, we obtained no useful information from the nasal swabs after we had made the preliminary survey of the types of staphylococci involved in the outbreak.

Clinical

The subsequent course of the epidemic is shown by the following numbers of lesions which appeared in successive months:

1959	November 1 to 15	39	41	1960	January	5
	" 15 to 30	2			February	5
	December	8				

Later Events

By February, 1960, conditions had so much improved that on February 29 various measures were relaxed. It was arranged that the use of intranasal naseptin cream, sponging in 1 in 5,000 hibitane solution after bathing, and nasal swabbing should be continued only in respect of patients with lesions. Members of the staff and patients without lesions were to be excluded from these measures.

There followed an immediate increase in the number of new lesions, which totalled 24 during March. We therefore reintroduced naseptin cream and sponging with hibitane for all the patients. During April nine new lesions occurred, during May 10, and during June only 3. In June, naseptin cream was again restricted to patients who had lesions, being applied while the lesions were present and for a few days afterwards. A gradual increase of new lesions was then seen, reaching a peak in August, after which the numbers fell spontaneously without any further action on our part. (This peak may have been wholly or in part a seasonal phenomenon associated with the warmer weather.)

The numbers of new lesions in successive months from June, 1960, to the time of writing were: June, 3; July, 8; August, 25; September, 18; October, 9; November, 9; December, 5; January (1961), 2; February, 5; March, 6.

Discussion

It is perhaps of some general interest that the epidemic was checked immediately without any form of segregation of the patients or staff, or of their belongings, and without isolation or barrier-nursing techniques. We cannot assess the relative values of the different measures we used, but our experience in March, 1960, led us to believe that the use of intranasal naseptin cream and sponging with hibitane 1 in 5,000 solution were playing an important part in holding the position at that time. We have seen no case of sensitization nor any other adverse effect from the use of these substances. It is regrettable that small numbers of new lesions continue to appear, but most of them are now papules or furuncles which heal in a few days, and only three boils have been seen during the first quarter of 1961. When one considers the nature of the unit these facts are not too disappointing.

Summary

An epidemic of cutaneous staphylococcal infections due to phage types 3B/3C+ and 80 occurring in a unit housing 30 mentally subnormal children was brought rapidly under control without any form of segregation, isolation, or barrier-nursing. The methods used are recorded.

We should like to pay a sincere tribute to the work of the nursing staff, particularly the sister-in-charge, Miss Mary Huston, who applied our suggestions with enthusiasm under conditions that could hardly have been less promising.

THE TRIPLE-X SYNDROME

CLINICAL, PATHOLOGICAL, AND CHROMOSOMAL STUDIES IN THREE MENTALLY RETARDED CASES

BY

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During the course of a survey of nuclear sex in a mental deficiency hospital, five patients with double sex-chromatin masses in their buccal mucosal cells were found (Ferguson-Smith, Handmaker, and Hill, in preparation). Two of these were phenotypic males with the clinical features of Klinefelter's syndrome, who were shown to have a chromosome number of 48 with an XXXY sex-chromosome constitution (Ferguson-Smith, Johnston, and Handmaker, 1960). The other three, who form the basis of this report, were females with 47 chromosomes.

Methods

The chromosome counts were performed on both bone-marrow and peripheral blood cells. The former technique is given elsewhere (Ferguson-Smith, Johnston, and Weinberg, 1960). The latter is based on a method originally described by Osgood and Brooke (1955) and modified by a number of workers. Thirty millilitres of the patient's blood are drawn into a heparinized syringe and placed in 10-ml. amounts in three sterile tubes, to each of which 0.25 ml. bactophytohaemagglutinin (Difco) is added; these are put in ice-water for one hour. After centrifuging for 10 minutes at 300–400 r.p.m. the opalescent plasma containing leucocytes is added in 3-ml. amounts to 2-oz. sterile prescription bottles containing 5 ml. of culture medium (NCTC 199 Difco). These are incubated for 66–80 hours. The cultures are treated in succession for the last two hours of incubation, with deacetylmethylcolchicine ("colcemid") to a final concentration of 1 μg./ml. After centrifugation at

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1,000 r.p.m. for five minutes the supernatant is discarded, and the deposit is incubated with 7 ml. of 1.12% sodium citrate for 15 minutes. Following centrifugation, 7 ml. of 50% acetic acid is used as a fixative. The deposit, with only a small quantity of the supernatant left after further centrifugation, is used to make air-dried smears as for blood films. These are stained with 2% aceto-orcein in 65% acetic acid, dehydrated, cleared, and mounted as usual.

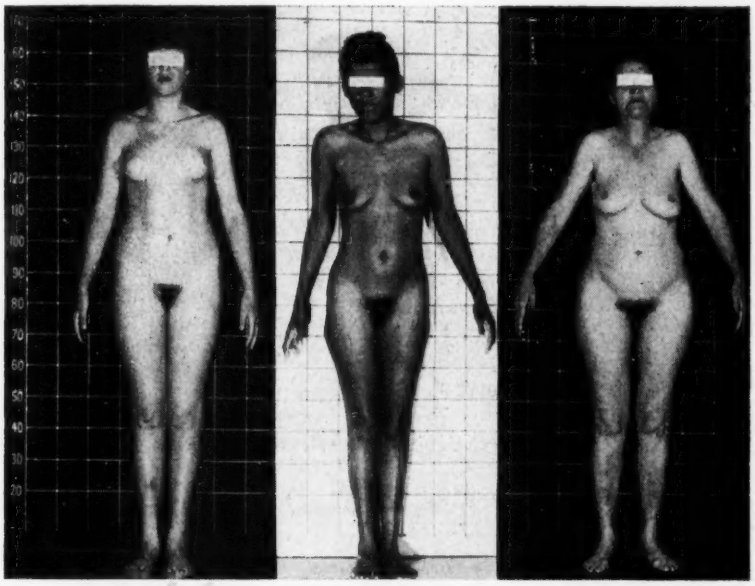

FIG. 1 FIG. 2 FIG. 3

FIG. 1.—Case 1, aged 14 years. FIG. 2.—Case 2, aged 26 years. FIG. 3.—Case 3, aged 39 years.

Urinary oestrogens were assayed by the method of Brown (1955), and urinary 17-ketosteroids by the method of Callow, Callow, and Emmens (1938).

Case Histories

Case 1

The patient was born on August 27, 1945. Her father was 33 and her mother 29 years of age at this time. There is one half-brother, aged 20, who has an infant daughter. The nuclear sex of the mother is normal.

She was admitted to a mental hospital in 1956. Her physical development has been normal, and she had her first and only recorded menstrual period in March, 1960, two months prior to laparotomy. Since 1949 she has had occasional seizures, usually in association with a high temperature.

Examination shows an unusually attractive but mentally retarded adolescent white female (Fig. 1). Her head is small, and she has a high-arched palate. The fingers are short and the little fingers are incurved, with only one interphalangeal crease on the right, while the left hand shows a transverse palmar crease (Fig. 4). There is bilateral optic atrophy and choroidoretinitis. The nervous system is otherwise normal. The breasts are normally developed. The external genitalia are normal and the vagina admits two fingers. The cervix is nulliparous, and the uterus is at the lower limit of normal in size. The adnexa are not palpable. Pubic and axillary hair are normal in amount and development. Systematic examination is otherwise normal. Radiological examination revealed a normal bone age and a brachycephalic skull.

Dr. John Money reported (May 21, 1960) that her I.Q. was less than 46 on the Wechsler intelligence scale for children. On the revised Stanford–Binet scale (Form L), an I.Q. of 18 was obtained. She can comprehend some of the events around her and can refer them appropriately, so that she will co-operate in most of the simple demands made of her.

Certain features suggest toxoplasmosis, particularly the choroidoretinitis in association with mental defect and epilepsy. The Sabin dye test was reported positive only at 1:64 dilution. The absence of intracranial calcification, and the relatively normal condition at birth, make this diagnosis uncertain.

Case 2

This patient was born on October 24, 1934. The father at this time was aged 33 and the mother 17. The latter is now confined to a State institution with a diagnosis of paranoid schizophrenia. A maternal aunt and uncle, in addition to a paternal aunt, have schizophrenia, while a maternal uncle is said to have general paralysis of the insane. There are four male sibs, all but one of whom are probably half-brothers. The three eldest have children. Both parents have normal nuclear sex.

The patient was admitted to a mental hospital in 1948 because of severe retardation. Her menstrual history is not well documented and her last menstrual period is not known, but she is stated to have periods at irregular intervals. Her general health is otherwise good.

Examination shows a severely retarded negro female of normal proportions (Fig. 2). She is hyperactive and cannot carry on a conversation. The head is small, with a high-arched palate and malocclusion of the teeth. The incisors are peg-shaped and she has marked gingivitis. Both pupils are irregular and react poorly to light and accommodation. There is a right corneal opacity. The tone is increased on the left, with increased reflexes in the left leg. Both plantar responses are flexor. The breasts are normally developed.

FIG. 4.—Case 1. Palmar aspect of the hands showing incurved fifth digits, one interphalangeal skin crease of fifth right digit, and left transverse palmar crease.

Axillary and pubic hair are normal, as are the external genitalia. The vagina admits one finger. The cervix is infantile and the uterus normally formed but small. The adnexa are small and free. Otherwise, physical examination shows nothing of note. A skull radiograph showed brachycephaly. The cerebrospinal fluid was normal and the *Treponema pallidum* immobilization test was negative.

Dr. John Money reported that it was not possible to obtain a value for her I.Q., her level being that of a mentally defective person of very low grade. In addition, he thought that she was having hallucinations and that the primary defect might be a congenital psychosis.

Case 3

This patient was born on August 27, 1921. Her mother was aged 18; nothing is known of the father. There are four living and apparently healthy half-sibs, and two others died in infancy for reasons now unknown. Three sibs of the mother are mentally retarded and two cousins have congenital deformities. The nuclear sex of the mother is normal.

She was admitted to a mental hospital in 1936. She menstruates regularly and her last menstrual period was about seven days prior to laparotomy.

Examination shows a moderately severely retarded white female of normal proportions who talks volubly (Fig. 3). There is good breast development, with normal distribution and amount of pubic and axillary hair. The external genitalia are normal. Pelvic examination reveals a normal vagina. The cervix and uterus are of normal size and in normal position. The adnexa are normal.

Her I.Q. on the Stanford–Binet scale was less than 31 (July 27, 1960), and her behaviour like that of a 4-year-old child.

Results

Chromosome Analysis

The majority of cells from both blood and bone-marrow in each patient showed 47 chromosomes (Table I). Detailed analysis of the 22 complete plates showed that the extra chromosome lay in Group III (Chromosome Nos. 7–12 and X) and fitted best into a triple-X pattern (Fig. 5). Five of the cells with fewer than 47 chromosomes were analysed. Different chromosomes were missing in each, suggesting loss of chromosomes by cell breakage during preparation. No evidence of chromosomal mosaicism was found.

TABLE I.—*Results of Chromosome Analyses*

		No. of Cells with Chromosome Count of:							Total	Plates Analysed			
		43	44	45	46	47	48	49		47	46	45	Total
Case 1	Blood		4	10	12	12	76		114 } 123	5	1		6
	Marrow					1	8		9 }				
,, 2	Blood	3	7	7	10	41		1	69 } 77	10	1		11
	Marrow		1	1	1	5			8 }				
,, 3	Blood	5	6	9	16	64	1		101 } 139	7	2	1	10
	Marrow	1		3	4	30			38 }				

Special Investigations

The results of some of the special investigations are recorded in Tables II, III, and IV.

TABLE II

	Case 1	Case 2	Case 3
Ovary size (cm.), L.	2·5×1·0×0·8	3·5×1·8×1·2	3·5×1·8×1·1 (7·5 c.cm.)
,, ,, ,, R.	3·0×1·5×1·0	3·0×2·5×1·2	3·0×2·2×2·1 (9·0 c.cm.)
Uterus size (cm.)	7·5×4·5×2·5	7·0×3·8×3·0	"Within normal" (not measured)
External genitalia	Normal	Normal	Normal
Secondary sex characteristics	,,	,,	,,
Ovarian histology, L.	Scanty follicles, undifferentiated stroma	Old corpus luteum, scanty follicles	,,
Ovarian histology, R.	Scanty follicles, follicular cyst	Scanty follicles	Recent corpus luteum
Endometrium ..	Non-secretory	Non-secretory	Secretory

TABLE III.—*Urinary Hormone Excretion/24 Hours*

	F.S.H. Mouse Units	17-Keto-steroids mg.	Oestrone µg.	Oestriol µg.	Oestra-diol µg.	Total Oestrogens µg.
Case 1	(a) <6·6	2·63	5	16	3	24
	(b) <6·6 <13·2 <26·4 <52·8	5·36	3	10	4	17
	(c)	2·2				
,, 2	(a) <6·6 <13·2 <26·4 <52·8	9·6	1	3	1	4
	(b) <6·6 <105·6	6·7	1	2	1	2
,, 3	(a) <13·2 <52·8 <105·6	1·8	10	11	6	27
	(b)	2·0				

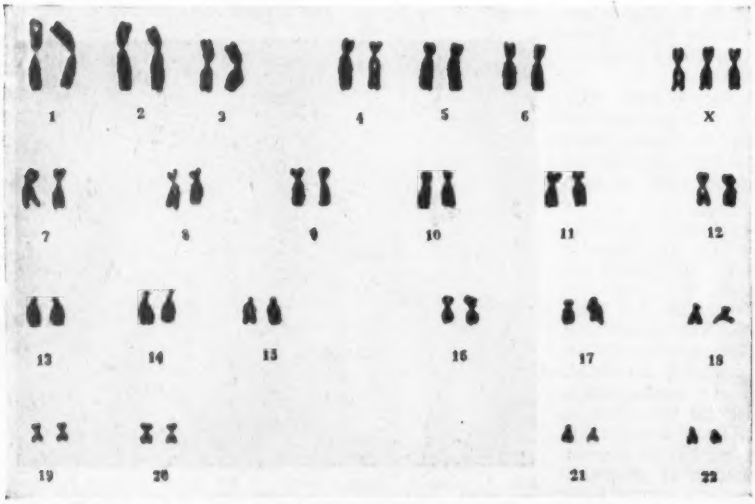

FIG. 5.—Karyotype of a peripheral blood cell in Case 2. 2n+1=47 (XXX).

At the time these studies were begun (May, 1960) only one other case with similar features was known. This case, reported by Jacobs *et al.* (1959), was that of a woman aged 35 with secondary amenorrhoea since the age of 19. She had double chromatin-positive nuclear sex and a somatic chromosome number of 47 with sex-chromosome constitution of XXX. In view of the gynaecological findings in this patient, it was decided to investigate the genital system of our patients as adequately as possible.

At laparotomy the internal genitalia were examined carefully, wedge sections were removed from the ovaries for histological examination, and endometrial biopsy material was

obtained. In each case the uterus was normal or somewhat smaller than normal (Table II), the Fallopian tubes were unremarkable, and there was no evidence of abnormal Wolffian derivatives. In Case 1 the ovaries were small (Fig. 6 and Table II), but in Cases 2 and 3 they were of normal size (Fig. 7).

On histological examination the ovarian stroma in Case 1 was poorly differentiated on both sides, and primordial ova were scanty, although a few maturing Graafian follicles were identified on the right (Fig. 8). Histological evidence of previous ovulation was not found in this patient. Ovarian follicles were also scanty in Case 2, despite normal-appearing ovarian stroma and evidence of an old corpus luteum. In Case 3 ova were seen in numbers consistent with the age of the patient, a recent corpus luteum was identified, and the ovarian stroma appeared normal (Fig. 9).

FIG. 6.—Case 1. Internal genitalia exposed at laparotomy. Small uterus, normal tubes, and hypoplastic ovaries. Right ovary almost entirely replaced by a simple follicular cyst.

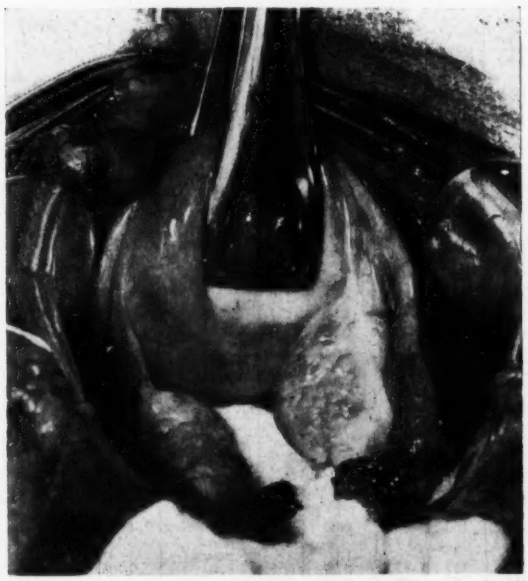

FIG. 7.—Case 2. Internal genitalia exposed at laparotomy. Small uterus, normal tubes, and normal-sized ovaries.

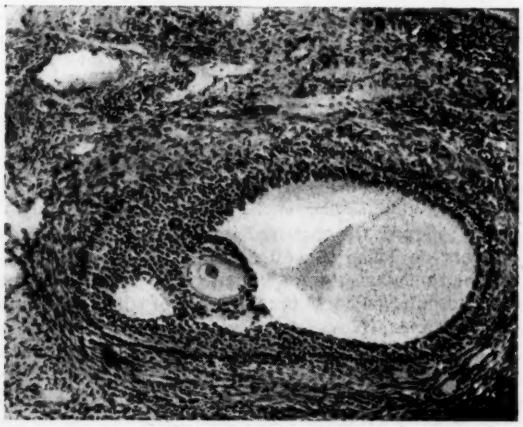

FIG. 8.—Case 1. Maturing Graafian follicle in right ovarian biopsy material. (Haematoxylin and eosin. ×85.)

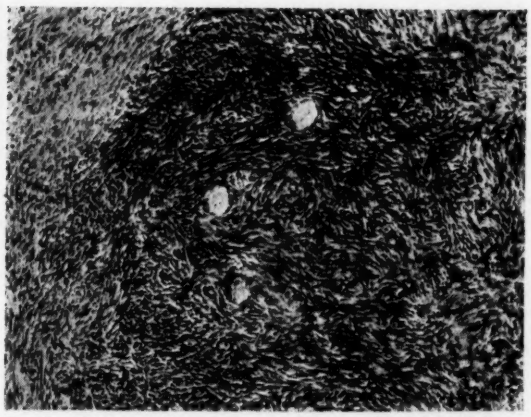

FIG. 9.—Case 3. Normal ovarian stroma with primordial ova in left biopsy material. (Haematoxylin and eosin. ×135.)

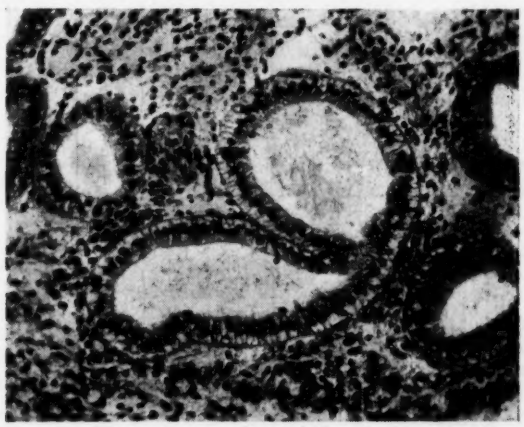

FIG. 10.—Case 3. Secretory endometrium in endometrial biopsy material at approximately 19th day of cycle. (Haematoxylin and eosin. ×203.)

In Case 3 an endometrial curetting obtained at the time of laparotomy contained insufficient tissue for diagnosis. An additional endometrial biopsy obtained on this patient three months after laparotomy on the 19th day of the cycle revealed an early secretory endometrium (Fig. 10), diagnosed as day-16 stage according to the criteria of Noyes *et al.* (1950) but nevertheless confirming continued ovulation. Endometrium obtained at laparotomy in Cases 1 and 2 showed no secretory changes.

A prominent feature of the histological material in all cases was the high incidence of two sex-chromatin masses in cell nuclei.

Discussion

Identification of the X Chromosome

We interpret the chromosome analyses in these three patients as being consistent with a trisomic-X sex-chromosome constitution, because in each case the extra chromosome belongs to a group of three pairs of chromosomes (Nos. 6, X, and 7) in which the X chromosome is normally found. The small differences in size and centromere position between these three pairs of chromosomes make it impossible to identify with absolute certainty the three X chromosomes in any given cell. However, circumstantial evidence that this is the correct interpretation may be derived from the abnormal sex-chromatin findings, for it has been the experience of most investigators that patients with a distinct nuclear-sex anomaly always have an abnormality of the sex-chromosome constitution. Although the origin of the sex-chromatin body must still be considered unsolved, available evidence relates it directly to part of a single X chromosome (Ferguson-Smith, 1960 ; Ohno and Makino, 1961).

We therefore feel justified in including in our list of known cases of the triple-X syndrome (Table IV) two cases each of which has a somatic chromosome number of 47 and double chromatin-positive nuclear sex, but which were not originally reported as triple-X cases. The patient of De Carli *et al.* (1960) was referred to as a "paramongol," and showed slanting palpebral fissures ; the additional chromosome was interpreted as an extra autosome in the 6–12 group, possibly homologous with the tenth or eleventh pair. The patient of Sandberg *et al.* (1960) was also studied because of apparent mongoloid facies ; in this case the abnormality was interpreted as trisomy of chromosome No. 6. It is possible that in these two cases the cytological findings are complicated by structural abnormalities of an X chromosome—that is, a deletion in the first instance and a translocation in the second instance. The recorded percentages of cells showing sex-chromatin bodies (Table IV) may possibly support such an explanation. For these and other reasons recorded elsewhere (Jacobs *et al.*, 1960a ; Ferguson-Smith, 1961a), we have included for purposes of comparison these two patients among the examples of the triple-X syndrome.

Clinical Features of the Triple-X Syndrome

It should be emphasized, before attempting to assess the phenotypic effect of the extra X chromosome, that the patients listed in Table IV, with three exceptions, were ascertained on account of mental defect. The sample is therefore a biased one. A completely satisfactory assessment of the syndrome will not be possible until the results of a large-scale nuclear-sexing survey of the general population are available. Such a survey would require a far larger sample than, for example, that of Moore (1959), who did not detect any triple-X cases in his survey of 1,804 newborn girls. The increased frequency of the condition among mentally defective patients is illustrated by the three cases described here, which were detected in a sample of 827 (0.36%) females at one mental deficiency hospital (Ferguson-Smith, Handmaker, and Hill, in preparation).

The additional X chromosome does not appear to have a consistent effect on sex differentiation. In only

TABLE IV.—*Known Triple-X Cases*

Age	I.Q.	Maternal Age	Paternal Age	Sibship Position	Menstrual History	Pregnancies	Single Sex Chromatin	Double Sex Chromatin	Drumstick Polymorphs	Height (cm.)	Lower Segment	Upper Segment/ Lower Segment	Span (cm.)	Special Clinical Features	Case No.	
35	? N	41	40	3/3	14–19 yrs. only	0	57	14	8/500	176	—	—	—	—	—	Jacobs *et al.* (1959)
21	M.D.	—	—	—	N	0	41	48	11/500	152	79	0·90	158	—	3	Jacobs *et al.* (1960b)
35	70	42	42	4/5	N	4	38	14	—	168	84	1·00	164	—	—	Stewart and Sanderson (1960)
19	70	34	39	—	N	—	49	8	—	167	—	—	—	"Paramongol"	—	De Carli *et al.* (1960)
21	40	41	49	4/?	N	—	?	70	5/100	172	—	—	—	Mongoloid facies. Webbed neck	—	Sandberg *et al.* (1960)
30	50	28	30	4/8	N	1	43	30	—	156	80	0·94	156	—	1	Fraser *et al.* (1960)
39	58	35	—	5/5	Irreg.	0	50	25	—	178	84	1·10	170	—	2	
61	38	40+	40–50	10/11	N	0	35	33	—	151	72	1·11	147	—	3	
73	50	—	—	2/3	—	0	33	30	—	156	77	1·02	154	—	4	
52	M.D.	34	33	6/7	13–17 yrs. only	0	—	—	—	155	78	0·92	156	—	S.S.	Jacobs, personal communication
47	M.D.	40	46	11/11	N	0	—	—	—	147	—	—	145	Acute encephalitis aet. 12 yrs.	J.H.	
18	? N	33	34	4/4	N	0	—	—	—	156	71	1·14	156	—	N.B.	
New born	? N	34	37	3/3	—	—	—	—	—	—	—	—	—	Normal child	B.R.	
23	M.D.	21	27	2/3	Two only	0	22	10	2/374	147	—	—	—	Spastic quadriplegia	M.S.	Hamerton *et al.*, personal communication
18	63	38	37	4/4	N (Irreg.)	0	54	8	"High" incidence	156	79	0·98	160	Nil	J.B.	Penrose, personal communication
15	46	29	33	2/2	? N	0	44	40	6/132	166	89	0·86	166	"Mongoloid" palms	1	Present communication
26	<20	17	33	1/1	Irreg.	0	38	50	6/123	163	85	0·91	166	—	2	
39	31	18	—	—	N	0	41	37	6/115	162	86	0·90	159	—	3	

four of the cases recorded in Table IV were the internal genitalia examined. In two cases the uterus was noted to be small, but this is unlikely to be significant. There is clearly no consistent abnormality of the ovary. In three cases the number of follicles was reduced, and in one case (Case 1) the ovaries were small and the ovarian stroma was poorly differentiated. In three cases out of 16 whose menstrual history is documented, secondary amenorrhoea is present, and in three others the periods are irregular. Of the 10 who have had a normal menstrual history, two are of proved fertility, despite the fact that they were detected during surveys of mental deficiency hospitals. Furthermore, our three patients are potentially fertile, since corpora lutea were found in two and normally maturing ova identified in the other.

The body proportions of these patients as assessed by height, span, and upper-segment/lower-segment ratios are unremarkable, and show no evidence of the disproportion noted in the XXY (Stewart *et al.*, 1959) and the triple X/Y (Ferguson-Smith *et al.*, 1960) cases, nor any striking evidence of short stature as in the XO cases of Turner's syndrome.

The only other clinical signs of note are the questionable mongoloid features which are present in three cases, and the webbing of the neck, which was found in one case. As webbing of the neck is a well-known feature of Turner's syndrome and has also been noted in one triple X/Y case (Ferguson-Smith *et al.*, 1960), it is of interest that it has been found in a third type of X-chromosome anomaly.

It is exceedingly difficult to compare the results of nuclear-sex determinations from different centres, as no two investigators have exactly the same criteria for counting. In the three cases reported here the numbers of "drumstick polymorphs" appear to be increased, the value for normal female blood smears being about 2–3%; no cells were identified with two drumsticks. In the buccal smears of our patients, double chromatin-positive nuclei were seen as frequently as single chromatin-positive nuclei, together giving a count twice the usual value for normal female smears.

The significance of the consistently low values for urinary 17-ketosteroids recorded in Table III remains unexplained. It is of interest that similar findings are noted by Carr *et al.* (1961) in their report on two mentally defective females with an XXXX sex-chromosome constitution.

Origin of the Triple-X Chromosome Abnormality

The data recorded in Table IV suggest that, as in mongolism, parental age may play a part in the aetiology of the condition.

The average maternal age of the 11 British patients is 35.1 years compared with a mean of 28.7 years (Penrose, 1961). The average age of eight of these fathers was 37 years compared with a mean of 32.2. The difference between mean of sample and expected = $35.1-28.7=6.4$ years. $t=\frac{6.4}{1.89}=3.39$ with 10 degrees of freedom. This is significant at the 0.01 level.

Similarly for the paternal age: The difference between mean of sample and expected $=37-32.2=4.8$ years. $t=\frac{4.8}{2.07}=2.32$ with 7 degrees of freedom. This is significant only at the 0.1 level.

If the mean increase in age of the fathers is corrected for regression on that of the mothers, it becomes only -0.2 year, which is clearly negligible. This suggests that the apparent increase in the father's age is only a reflection of that of the mother. However, the opposite interpretation—that the apparent increase in the mother's age is only a reflection of the father's—seems less plausible. The increase in the mother's age after correction for regression on the father's becomes 3.2 years, which is not significant in such a small sample.

The trend to a higher than average maternal age is supported by the records on sibship position, which indicate that out of 14 families, the propositus was the last-born child in eight and the second last in five. The accumulation of data from a greater number of cases from the general population is clearly desirable.

With regard to the origin of sex-chromosome aneuploidy in general, cytological studies of human meiosis in testicular material (Ford and Hamerton, 1956; Kodani, 1958; Ferguson-Smith, 1961b) raise the possibility that precocious disjunction of the sex chromosomes at the first meiotic division is one of the most likely explanations. Gametes bearing both sex chromosomes, or neither, may also arise by failure of the sex chromosomes to pair at the first meiotic division, or by non-disjunction of the sex bivalent; however, it is impossible at present to demonstrate which one of these various explanations is correct. So far as the triple-X patients are concerned, the parental age data might be interpreted as evidence in favour of the defect arising during oogenesis. On the other hand, the existence of XO/XXX mosaicism (Jacobs *et al.*, 1960b) might well be interpreted as good evidence for another possible mechanism—namely, mitotic non-disjunction in the zygote with elimination of the XO cell line.

As most cases of triple-X syndrome are fertile, or potentially so, theoretically the normal process of chromosome segregation during meiosis should produce equal numbers of ova containing one and two X chromosomes. When fertilized by normal sperm the abnormal XX ova will give rise to XXX and XXY individuals.* As the nuclear sex of all the offspring and all the parents of the triple-X cases so far tested has been normal, there is no evidence that this type of familial transmission occurs. It may be that in the fertile triple-X cases there is selection in favour of normal ova or zygotes.

Conclusion

No consistent clinical pattern can be distinguished in the examples of the triple-X syndrome at present available. While a high proportion of cases may be seen on account of mental or gynaecological disturbances, there remains the possibility that cases exist in the general population without recognizable clinical abnormality, and detectable only by nuclear-sex determination and chromosome analysis.

Summary

Clinical and chromosomal studies are reported in three mentally defective individuals with the triple-X syndrome. Histological evidence of normally maturing

*Where the two X chromosomes are those that were involved in primary non-disjunction in the mother, this situation is correctly referred to as secondary non-disjunction as originally defined (Bridges, 1913). Where both the X chromosomes are not those that failed to disjoin primarily, the trisomy is not strictly the product of secondary non-disjunction but of normal segregation.

ova in each, and the additional finding of corpora lutea in two, indicate that these patients are potentially fertile. Examination of clinical and laboratory data of all similar cases at present available fails to reveal a characteristic syndrome related to the presence of an extra X chromosome and distinguishable on clinical grounds.

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STUDY OF CHROMOSOMES IN HUMAN LEUKAEMIA BY A DIRECT METHOD

BY

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Since the first reports (Ford *et al.*, 1958; Nowell *et al.*, 1958) of chromosome studies in human leukaemia, great interest has centred on this problem. The findings of different workers have varied considerably, especially with regard to acute leukaemia, where numerical and/or structural abnormality was found in one of the three cases studied by Ford *et al.* (1958), in four of the five cases reported by Baikie *et al.* (1959), and in three of the five cases recorded by Sandberg *et al.* (1960). On the other hand, normal findings have been reported by Nowell and Hungerford (1960a) in three cases of acute leukaemia, by Bayreuther (1960) in five cases, while Tough *et al.* (1961) recorded no abnormality (apart from the trisomy of autosome 21) in five cases of acute leukaemia occurring in mongols.

There is more agreement regarding the situation in chronic leukaemia, the majority of reports of which agree that there is probably no numerical abnormality. As regards structure, however, Nowell and Hungerford (1960a, 1960b) reported that in seven cases of chronic myeloid leukaemia one of the smallest autosomes (21 pair, Denver classification), was much reduced in size. This observation by the Philadelphia workers has been confirmed by the Edinburgh group (Baikie *et al.*, 1960a; Tough *et al.*, 1961), who found this minute chromosome, termed by them the Ph^1 chromosome, in 13 out of 18 cases of chronic myeloid leukaemia.

We report here a study of 16 cases of leukaemia in which a direct non-culture technique of preparation (Kinlough *et al.*, 1961) has been employed. In this way some of the difficulties of interpretation of culture results (Ford and Mole, 1959) have been avoided. In this study an abnormality of chromosome number has been found in two of the eight cases of acute leukaemia studied, while the presence of the Ph^1 chromosome has been confirmed in two of the four cases of chronic myeloid leukaemia.

Methods

Throughout this investigation a deliberate attempt was made to obtain samples for study, either from bone-marrow or from peripheral blood, before any antileukaemic treatment had been given. This was successful in all but three instances.

The methods employed have been previously reported (Kinlough *et al.*, 1961). In the earlier part of this work colchicine (0.1 mg./kg. body weight) was injected intravenously one hour before bone-marrow aspiration. (This was felt to be permissible in leukaemic cases.) Later it has been found that the use of E.D.T.A. (dipotassium (ethylene-dinitrilo) tetra-acetate) as an anticoagulant into which the marrow or blood cells are received renders the use of colchicine unnecessary, since E.D.T.A. appears to have a marked colchicine-like

effect on chromosomes, producing well-differentiated metaphase plates (Kinlough and Robson, 1961). The marrow aspirate or peripheral blood leucocyte concentrate is suspended in hypotonic citrate for 10 minutes and then fixed for two hours in acetic-alcohol. Hydrolysis is then carried out in N HCl for six minutes at 60° C. The cells are then resuspended in 45% acetic acid, and, from this, squash preparations stained with acetic-orcein or with Feulgen are made.

Results

Clinical and haematological details of the 16 patients studied are given in Table I. In eight (six male, two female) the disease was acute in type and course, while the remaining eight patients suffered from the chronic variety—four myeloid and four lymphatic in type.

TABLE I.—*Clinical and Haematological Data in 16 Cases of Leukaemia*

Case No.	Sex	Age (Yr.)	Type of Leukaemia	Estimated Duration of Disease (Months)	Date of Chromosome Study	Peripheral W.B.C./c.mm. (% Main Cell)	Anti-leukaemic Treatment before Study
1	M	79	Subacute myelomonocytic	18	25/5/60	30,000 (Mon. 70%)	None
2	F	42	Stem-cell	1	2/8/60	14,000 (Bl. 90%)	,,
3	M	52	Acute myeloid	3	2/9/60	8,000 (Bl. 5%)	,,
4	M	29	,, ,,	1	22/9/60	10,000 (Bl. 22%)	6 M–P
5	M	32	,, ,,	3	3/3/61	146,000 (Bl. 98%)	None
6	M	34	,, ,,	1½	12/3/61	86,000 (Bl. 100%)	,,
7	F	61	,, ,,	3	15/3/61	39,000 (Bl. 90%)	,,
8	M	18	,, ,,	1	15/3/61	20,000 (Bl. 50%)	,,
9	M	40	Chronic myeloid	18	22/9/60	110,000 (P. 72%)	None
10	M	61	,, ,,	24	23/11/60	42,000 (P. 60%)	,,
11	F	76	,, ,,	6	7/2/61	210,000 (P. 49%)	,,
12	M	45	,, ,,	9	19/5/61	28,000 (P. 68%)	Busulphan
13	F	72	Chronic lymphatic	24	17/5/60	200,000 (L. 80%)	None
14	M	55	,, ,,	1 (?)	19/9/60	36,000 (L. 82%)	,,
15	M	59	,, ,,	24	22/9/60	430,000 (L. 99%)	,,
16	F	50	,, ,,	24	1/10/60	9,400 (L. 30%)	DXR Chlorambucil

Bl. = myeloblast; P. = polymorph leucocyte; Mon. = monocyte. 6 M–P = 6-mercaptopurine; DXR = radiotherapy.

Acute Leukaemia (Cases 1 to 8)

The results of chromosome study in these cases are summarized in Table II. Here it may be seen that six (Nos. 1, 2, 3, 4, 6, and 8) of the eight cases studied showed no significant variation from the normal diploid number of 46. Detailed karyotype study in these cases revealed no constant structural abnormality. Two cases, however, were abnormal (Nos. 5 and 7). In both there was a predominant chromosome number of 47, such cells making up 77% of the total scored in Case 5 and 69% in Case 7. Detailed examination of these cells revealed a constant abnormality in karyotype. The karyotypes of the two cases are shown in Figs. 1 and 2 respectively.

TABLE II.—*Chromosome Counts in Eight Cases of Acute Leukaemia*

Case No.	41	42	43	44	45	46	47	48	>48	Total
1	1	1	1	1	5	48	2	3	1	63
2	1	2	—	4	3	18	—	1	1	30
3	—	1	4	4	1	24	3	—	—	37
4	—	2	—	3	1	19	—	—	—	25
5	—	2	—	3	2	11	79	6	—	103
6	1	3	2	2	4	113	7	1	—	133
7	—	—	—	—	—	5	24	6	—	35
8	—	2	—	1	3	40	—	—	—	46

The extra chromosome (marked "A" in Figs. 1 and 2) was very similar in both cases. It was of medium size, of the order of the pairs 13–15 of the Denver classification. This extra chromosome, in the cells of both cases, stained densely and showed little arm repulsion. Both patients whose cells showed this abnormality suffered from acute myeloid leukaemia, which had been present for a relatively long period

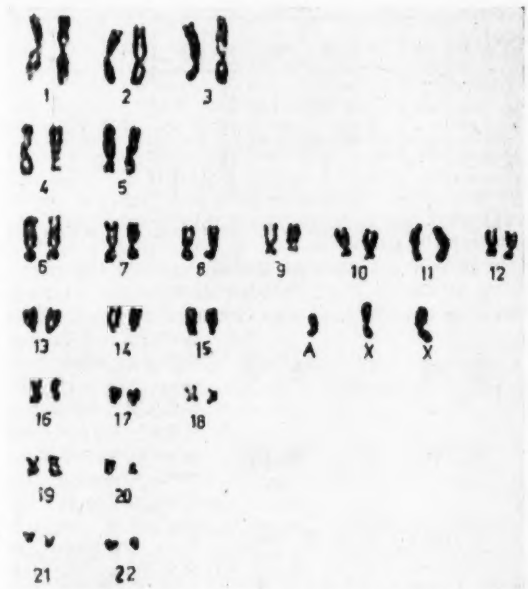

FIG. 1.—Karyotype of Case 5 (acute myeloid leukaemia) showing chromosome complement of 47. The additional chromosome is marked "A."

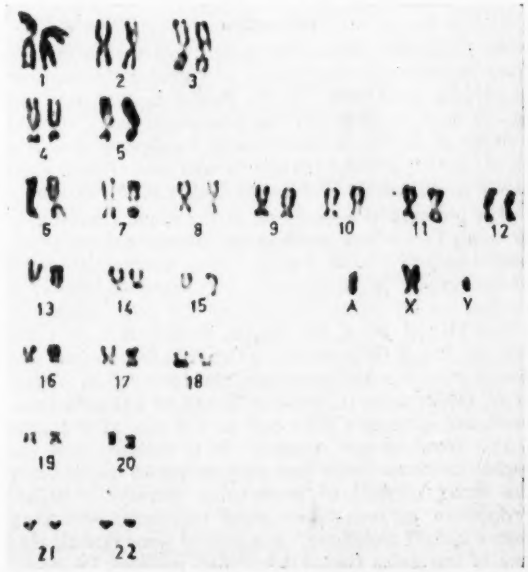

FIG. 2.—Karyotype of Case 7 (acute myeloid leukaemia). The additional chromosome is again marked "A."

(three months) when examined. Neither patient had received any treatment prior to chromosome examination (Table I).

Chronic Leukaemia (Cases 9 to 16)

The findings in these cases are summarized in Table III. Examination by the direct technique was more tedious because of the sparser number of mitotic figures. In most cases, however, adequate numbers of suitable cells were found. No numerical abnormality was found in any of these chronic cases; all in fact showed a predominant chromosome count of 46.

TABLE III.—*Chromosome Counts in Eight Cases of Chronic Leukaemia*

Case No.	41	42	43	44	45	46	47	48	>48	Total
9	—	—	—	3	1	21	—	—	—	25
10	2	3	—	—	1	52	—	—	—	58
11	—	—	—	2	1	40	—	—	—	43*
12	—	—	2	—	—	50	2	2	—	56†
13	—	—	—	—	—	10	—	—	—	10
14	—	—	1	1	2	34	1	—	—	39
15	—	—	1	2	2	44	1	—	—	50
16	—	2	3	1	4	50	1	—	—	61

* 39 of these cells contained the Ph¹ chromosome. † 51 of these cells contained the Ph¹ chromosome.

In two of the cases of chronic myeloid leukaemia, Cases 11 and 12, the "Philadelphia chromosome" was found in over 90% of cells examined in detail. This is illustrated in Fig. 3. The other two cases of chronic myeloid leukaemia (Cases 9 and 10) were examined at an early stage of this investigation, and the quality of preparations obtained at that time does not permit a decision on whether this abnormality was definitely present or not.

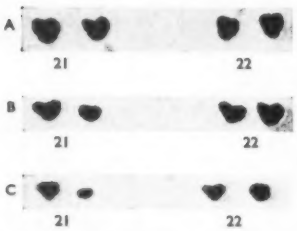

FIG. 3.—A, Chromosome pairs 21 and 22 in a normal subject; B, from Case 11; C, from Case 12, showing the Ph¹ chromosome in chronic myeloid leukaemia.

Discussion

As mentioned earlier, the majority of studies to date have reported no abnormality of chromosome number in chronic leukaemia. In the present investigation, all of the eight cases of chronic leukaemia had a diploid number of 46, which accords with the reports of Baikie *et al.* (1959, 1960b, 1961c), Nowell and Hungerford (1960b), Bayreuther (1960), and Tough *et al.* (1961).

The presence of a structural chromosome abnormality in cases of chronic myeloid leukaemia, however, has been confirmed in this study. The abnormally small autosome 21 (Denver)—the Ph¹ chromosome—was present in the great majority of the cells studied in Cases 11 and 12 of the present series. It is of some interest that in these two cases the Ph¹ chromosome was found in higher incidence than that recorded by Tough *et al.* (1961), who found it in 98 out of 132 cells from untreated patients (74%) and in 178 out of 283 cells (63%) from treated patients. It is believed that the higher incidence found here may be due to the fact that the direct method of preparation displays a higher proportion of metaphases from leukaemic cells than does a culture technique. It is also of some interest that one of our cases (No. 12) had had previous treatment with busulphan, which did not seem to have reduced the incidence of the Ph¹ chromosome. This contrasts with the effects of radiation, which, according to Tough *et al.* (1961), reduced the proportion of cells containing the Ph¹ chromosome. It is not possible to offer comment of any weight on the intriguing suggestion of the Edinburgh workers (Tough *et al.*, 1961) of a relationship between the Ph¹ chromosome and the trisomy of pair 21 in mongolism. The Ph¹ chromosome was not found in any of the acute cases in the present series. Leukaemia in mongolism is usually acute, and the Edinburgh group themselves found only the expected trisomy in five cases of acute leukaemia in mongols.

The position as regards chromosome patterns in acute leukaemia is confused. It has been suggested (*Lancet*, 1961) that there is no specific pattern and that changes which have been observed are simply the irregularities to be expected in malignant tumours. This is certainly plausible, and derives support from situations such as the one described by Tough *et al.* (1961) where their Case 17, in acute transformation of chronic myeloid leukaemia, was found to have developed a hyperdiploid cell line with 49 chromosomes. (It may be noted that this patient had previously had radiotherapy.)

If chromosomal abnormality was simply an expression of the degree of malignancy the incidence and variety of such abnormality might be expected to correlate roughly with the acuteness of the leukaemia. No such correlation is evident at the present time. So far, studies of some 26 cases of acute leukaemia have been reported by various workers. Of these, normal findings have been reported in 13 cases, and a variety of numerical and structural changes in 10. From the information available it does not appear that the abnormal cases were more acute, either clinically or haematologically, than were those found to be normal. In the present series the two cases with abnormal chromosome complements were distinguished by the fact that the course of the disease was rather less acute than in other cases of the group in which the chromosome number was normal. It is also somewhat surprising to find that both cases had the same abnormal number and that the extra chromosome was so similar in the two cases. Although both cases were of the acute myeloid type, one was a male aged 32 years and the other was a female aged 61. Neither had had any antileukaemic treatment. Similar features of age, sex, and absence of previous treatment were observed in other cases of the series in which the findings were normal. Unfortunately, attempts to culture skin from the two abnormal cases were not successful. However, both patients were normal in physique, development, and sexual function, and an inherent trisomic state seems improbable.

For the reasons stated above we are reluctant to accept entirely the suggestion that these findings in acute leukaemia are merely expressions of the disorder of neoplasia. The remarkably different findings of different groups of workers are perhaps reflected in the findings in this series, where six cases were unequivocally normal and two cases impressively abnormal. Just as the chromosomal situation in chronic myeloid leukaemia appears to be different from that in chronic lymphatic leukaemia, we are tempted to speculate on whether there may be similar differences in different groups of acute leukaemias. Despite the notorious difficulty in identifying the haematological type in acute cases, it would seem desirable to attempt to do this in association with further chromosomal studies.

The development of the direct method for the study of the chromosomes of human leukaemic cells was

prompted by the thought that in leukaemia the cells of the bone-marrow are in a state of frequent division. Therefore it should be feasible to take advantage of this situation in order to avoid the possibility of non-representational development in the artificial conditions of *in vitro* culture. A similar approach was indicated by Sandberg *et al.* (1960) and a similar technique described by Bottura and Ferrari (1960).

The method employed in the present study has proved to be simple and effective, especially in cases of acute leukaemia. As might be expected, the ease with which an adequate number of suitable metaphases can be found is proportional to the degree of marrow activity, as judged on haematological grounds.

A number of authors (Baikie *et al.*, 1959; Ford and Mole, 1959; Nowell and Hungerford, 1960a) have discussed the question of whether the results of culture, even short-term, are representational. The last-named authors, for example, concluded that the relatively long period of colchicine treatment employed by them was responsible for the production of hypodiploid forms in preparations from both normal and leukaemic subjects. These problems of interpretation of findings after culture are avoided by a direct method of preparation. When this is used it may be concluded with some certainty that the findings represent the situation in the cells of the marrow or of the blood at the moment of sampling.

Summary

A method is described which permits the direct study, without culture, of the chromosomes in cells from bone-marrow or from blood.

The study, by this method, of chromosome patterns in 16 cases of leukaemia is described.

The normal diploid number was found in all of the eight cases of chronic leukaemia studied. The abnormally small Ph^1 chromosome was definitely present in two of the four cases of chronic myeloid leukaemia. No abnormality was found in four cases of chronic lymphatic leukaemia.

In six of the eight cases of acute leukaemia studied the chromosomes were normal in number and in structure.

A predominant chromosome complement of 47 was found in two cases of acute myeloid leukaemia. The extra chromosome was of similar character in each case.

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CHROMOSOME DAMAGE DURING NITROGEN MUSTARD THERAPY*

A CASE REPORT

BY

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A great quantity of literature has been accumulated on the effects of radiation and radiomimetic substances upon cells. Much of this work has been done on mammalian tissues both *in vivo* and in tissue culture. Some of these damaging effects can be seen by examination of these cells during their division. Abnormal mitoses are common, with an unusual stickiness of the chromosomes and frequent anaphase-lagging. Structural changes may be seen in the chromosomes as either chromatid or chromosome deletions, the production of fragmented chromosomes, and the production of abnormal-shaped chromosomes, particularly ring forms and dicentrics. These changes have been demonstrated in human tissues during culture by Puck *et al.* (1957).

After the development of a technique for tissue culture of human peripheral blood, Tough *et al.* (1960) were able to demonstrate abnormal chromosome numbers and patterns in cultures from patients who had received irradiation therapy. Even a single radiation dose of 250 rads produced chromosome changes in a patient receiving therapy over the spine for spondylitis.

We wish to report the case of a patient who showed chromosome abnormalities in the cells cultured from peripheral blood after nitrogen mustard therapy for malignant disease.

Case Report

A 62-year-old man was admitted with fatigue, anorexia, and epigastric pain. He noticed the fatigability and accompanying signs of dry skin and constipation two years before admission, when he first sought medical advice. A hypothyroid condition was diagnosed and 3 gr. (0.2 g.) of thyroid was administered daily. More recently the patient had epigastric pain radiating to the back for a period of three months. He had lost 20 lb. (9 kg.) in weight over a two-year period and weighed 135 lb. (61 kg.) on this admission.

Physical examination showed nothing of note, but a chest radiograph revealed a mass in the left lower lobe. This radiograph was compared with previous chest plates taken two years, one year, and six months previously. The mass was visible on the film taken six months previously although it was then much smaller. Bronchoscopic examination was negative, but bronchoscopic washings showed malignant cells to be present. Tomograms showed the lesion to be approximately 5 cm. in diameter and to involve the subapical segment of the left lower lobe, and there was also hilar enlargement on the left side.

A scalene lymph-node biopsy showed the presence of metastatic carcinoma. Treatment was begun with 12 mg. of nitrogen mustard given intravenously. This was followed one week later by a course of radiotherapy with a tumour dose of 1,200 r per week for three weeks.

*This study was supported by funds from the Ontario Cancer Research Foundation, a Federal Provincial Health Grant, and the Research Institute, Hospital for Sick Children.

The patient died seven weeks after the starting of treatment, and at necropsy a bronchogenic carcinoma arising in the left lower lobe, with metastases in both adrenal glands and the para-aortic lymph nodes, was found.

Chromosome Studies

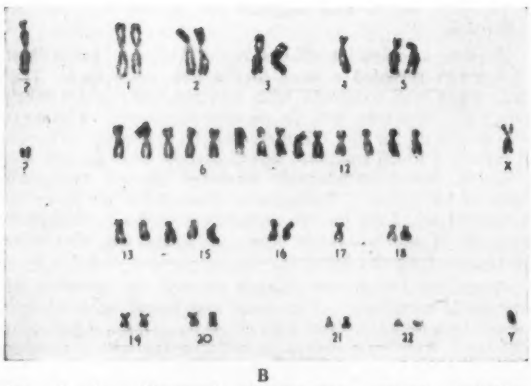
Chromosome preparations were made from peripheral blood samples by a modification of the method described by Moorhead *et al.* (1960). One sample was taken before treatment, and two further samples were taken after nitrogen mustard treatment but before radiation treatment had begun. The effects of nitrogen mustard treatment upon leucocyte chromosomes were investigated by comparison with the control samples before treatment. The findings are summarized in the accompanying Table, and showed a normal chromosome number and XY sex-chromosome complement in the cells before treatment was started and a greater variation in chromosome numbers and structural abnormalities of the chromosomes after treatment. The culture taken two days after the nitrogen mustard treatment failed to provide enough cells in mitosis for any worth-while analysis. The few that were present were unsuitable for accurate counting and appeared to be shrivelled. The paucity of mitoses was probably related to the leucopenia usually produced by this treatment. The culture prepared from blood taken four days after the nitrogen mustard provided many mitoses suitable for detailed examination. Abnormal chromosomes were present and included fragments (F) and dicentrics (D) (Fig. 1,A).

Days After Dose	*Total Cells Counted	Distribution							Chromosome Structural Change		
		<44	44	45	46	47	48	4n	†No. of Cells Examined	No. of Cells Abnormal	% Abnormal
−6	25			2	23			<1%	50	0	0
+2	None										
+4	76	2	3	3	64	4		<1%	160	7	4·5

* Does not include cells with a visible structural chromosome abnormality.
† Includes "total cells counted."

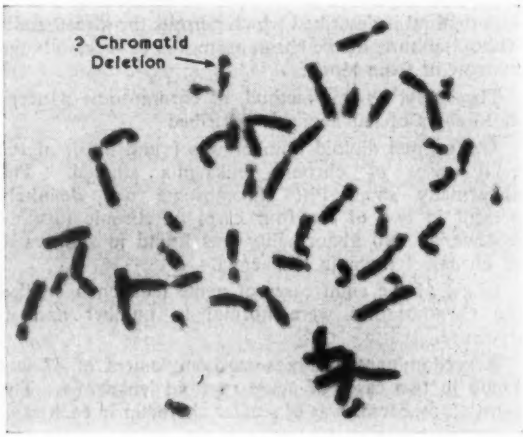
Fig. 2 shows examples of other chromosomes of unusual shape that were found. Fig. 2,A appears to represent a chromatid deletion of a chromosome in the 13–15 group, although we have on rare occasions seen this phenomenon in cultures from patients where there was no known history of exposure to *x* rays or radiomimetic agents. Fig. 2,B appears to represent a fusion of three chromosomes. No ring chromosomes or tricentrics were seen. Analysis of cells showing chromosome damage is very difficult and interpretation uncertain, so that only a partially analysed karyotype is shown in Fig. 1,B.

A

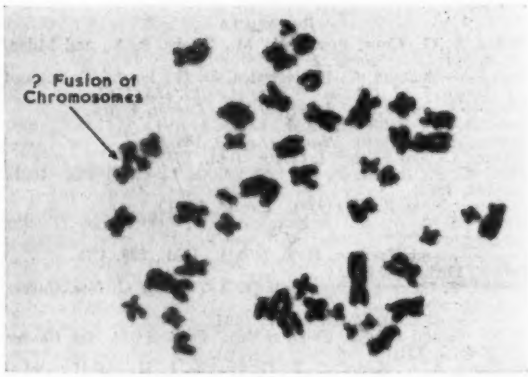


B

Fig. 1.—A: Abnormal chromosomes present, including fragments (F) and dicentrics (D). B: Partially analysed karyotype.



A



B

Fig. 2.—A: Showing ? chromatid deletion. B: ? Chromosome fusion.

The value of chromosome counts in this type of case is difficult to assess. Total counts in cells with structural chromosome changes are sometimes uncertain, since unusual shapes may be formed, causing difficulty in interpretation. Fragments are conventionally counted as a chromosome by most but not all workers. In cultures from cases without radiomimetic damage, the significance of chromosome counts differing from the modal number can be partially tested by analysing them to see if the abnormal count is consistently associated with an abnormal number of chromosomes in one group. In the type of case presented this precaution is not possible, because the radiation would also damage different groups of chromosomes. Very large numbers of cells should be counted before alterations of the modal-cell percentage can be regarded as significant. However, in this laboratory it has been noted that cell breakage during chromosome preparation only rarely produces cells with counts above the modal number, whereas some cells are usually found with counts below this number. But in this case, and in other cases receiving radiomimetic agents, a significant number of counts above the modal number has been observed. The technique of air-drying the cells to obtain flattening, which is so successful with tissues grown directly on glass, greatly reduces the number of broken cells (Rothfels and Siminovitch, 1958). However, it does not seem to give so many good clear metaphase plates as the squashing method, when applied to cultures of blood or marrow.

Tough *et al.* (1960) found a considerable increase in polyploid cells after irradiation. In one patient the incidence of polyploids was normal four days after irradiation, then increased and remained elevated for many days. The second patient showed many polyploid cells the day after treatment, but the incidence fell to normal levels until a second increase in polyploid cells occurred one week later. Boyd *et al.* (1961) reported chromosome aberrations after radioiodine treatment and also noted an increased incidence of tetraploid cells. There was no noticeable increase in tetraploid cells in the culture made four days after giving nitrogen mustard in our case. Further samples at different time intervals might have shown an increased number of tetraploid cells.

Discussion

The increase in percentage of non-modal chromosome counts compared with the pretreatment control counts is related to the radiation-type damage. If only the cells with apparently intact chromosomes are counted this will include only part of the population of cells with chromosome damage. Cells containing structural chromosome abnormalities are easily recognized, and a large number of cells can be examined quickly without chromosome counts. Probably a far larger number of cells show no visible evidence of chromosome damage and repair, and will escape detection. However, a combination of the non-modal chromosome counts and the numbers of cells showing chromosome damage will give a low estimate of radiation damage. The use of examinations for structural abnormalities should be stressed, since cells can be screened by a technician and "suspicious" cells checked by a more experienced worker.

The chief significance of this report is that, if nitrogen mustard can cause chromosome aberrations in leucocytes, abnormalities may also be produced in the germ cells, since the nitrogen mustard is carried to all parts of the body. Some slight control of the distribution of this agent is possible by using the recently developed regional perfusion techniques. Although the side-effects of this drug are severe for many hours, it is possible that an abnormal zygote could be conceived in the few days following the radiomimetic damage to the germ cells. This would be more likely after treatment of males, since a female with malignant disease would be less likely to conceive or carry a child to term. The problem of the relationship between radiomimetic agents and the later development of leukaemia is of academic interest only because of the prognosis expected in this type of case.

Summary

Chromosome studies were made on blood samples from a patient with malignant disease before and during nitrogen mustard therapy. Structural chromosome abnormalities were demonstrated in these leucocyte cultures. Nitrogen mustard is widely distributed in the body and presumably could cause similar damage to the germ cells. This might provide a mechanism for the formation of an abnormal zygote.

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ATHEROMA OF THE CAROTID AND VERTEBRAL ARTERIAL SYSTEMS

BY

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The importance of disease of the neck arteries in the causation of strokes was first appreciated last century (Todd, 1844; Gull, 1855), and was emphasized by Ramsay Hunt (1914); but, in general, the condition of the intracranial arteries was still held to be the most important factor. The introduction of angiography and the practicability of surgical intervention has tended to reverse this view by focusing increasing attention on the neck arteries. Hutchinson and Yates (1957) stressed the importance of considering the carotid and vertebral systems together, and reported that of 83 patients with cerebral vascular symptoms 40 had marked narrowing of one or more of the neck arteries.

We felt that in order to put this finding into perspective it was important to assess the condition of the neck arteries in a consecutive and unselected series of necropsies. We have studied 93 such patients and report here our findings, with respect to the severity and localization of atheroma, the frequency and site of stenosis, and the presence of occlusion and ulceration.

Methods of Study

The carotid and vertebral systems were removed from every fifth patient over the age of 35 on whom a

necropsy was performed at the Radcliffe Infirmary, Oxford, in the period February–June, 1960. The aortic arch, innominate artery, subclavian arteries, and cervical parts of the internal carotid arteries were dissected free. Then the intracranial course of the internal carotid arteries was exposed by removing the overlying sphenoid and petrous temporal bones, and the arteries were gently mobilized. The foramen lacerum was enlarged and the vessels were drawn through into the neck. The bony course of the vertebral arteries was exposed by removing the transverse processes of the second to sixth cervical vertebrae and the posterior arch and transverse processes of the atlas vertebra. The arteries were freed from their bony canals and cut just below the origin of the basilar artery. We now had a single block of tissue containing the four systems supplying the brain. The arteries removed are shown in Fig. 1.

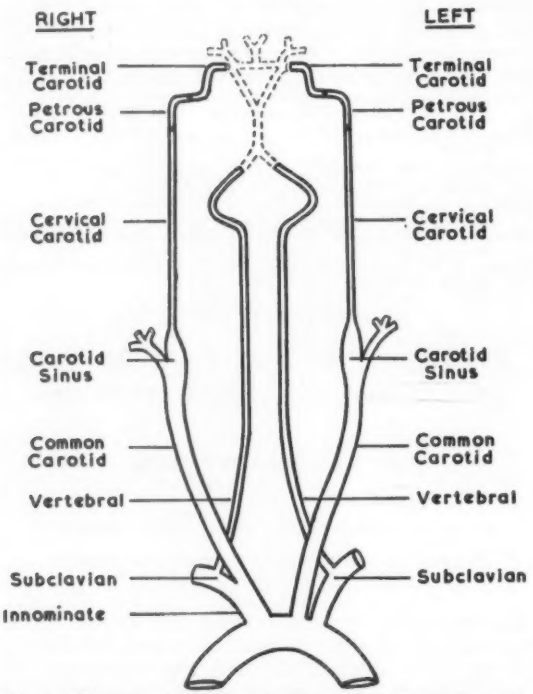

FIG. 1.—Diagram of carotid and vertebral arterial systems. The vessels removed for examination are shown by an unbroken line.

After adventitial debris had been removed, the specimen was washed in 0.9% sodium chloride solution and fixed in 10% formalin. The arteries were then opened by cutting longitudinally along their anterior aspect and assessed jointly by the two observers with respect to (1) atheroma, (2) stenosis, (3) occlusion, and (4) ulcerating lesions. Each named segment of the four systems was graded separately. (The internal carotid artery is divided by anatomical convention into four parts: (*a*) cervical, (*b*) petrosal, (*c*) cavernous, (*d*) cerebral. We have amalgamated the latter two segments for grading purposes and called this the "terminal carotid.")

Atheroma was graded by visual estimation of the proportion of the total surface area of each opened segment which was abnormal. Four arbitrary grades were used: (*a*) Free: no macroscopic abnormality. (*b*) Slight: less than 10% of the total area abnormal. (*c*) Moderate: 10–50% of the vessel surface abnormal. (*d*) Severe: more than 50% abnormal.

Stenosis was assessed by cutting serial transverse sections through abnormal segments, and three grades were used as recommended by the W.H.O. Study Group (1958): (*a*) No stenosis. (*b*) Moderate stenosis: appreciable reduction in the size of the arterial lumen, but more than half the diameter of the original lumen remains. (*c*) Severe stenosis: less than half the diameter of the original lumen remains.

To identify the site of stenosis each named part of the arterial tree, except the carotid sinuses, was divided into proximal, middle, and distal thirds. Where stenoses were found in two or more thirds, multiple stenosis was recorded.

Ulceration and occlusion were noted and the affected areas removed for histological examination. In assessing the atheroma and stenosis grading, if the observers were in doubt or disagreed the less severe of the two possible grades was recorded. The aorta was removed from each of the patients studied, stripped of adventitial debris, opened longitudinally along its anterior aspect, washed in 0.9% sodium chloride solution, and the segment between the upper paired intercostal arteries and the aortic bifurcation fixed in 10% formalin solution. This segment was stained with Sudan IV (Holman *et al.*, 1958) and its total area and the areas occupied by fatty streaks, fibrous plaques, raised fatty lesions, and complicated lesions (ulceration, calcification, or thrombosis —W.H.O., 1958) assessed by tracing the aortic outline and that of the lesions on waterproof tracing-paper and measuring their area planimetrically. This method will be described in detail elsewhere.

Results

Composition of Necropsy Sample

The Age-and-sex Distribution of the 93 patients is shown in Table I.

TABLE I.—*Age-and-sex Distribution of the 93 Patients Studied*

Group	Age (Years)						Total
	35–44	45–54	55–64	65–74	75–84	85+	
Males	4	4	18	13	10	4	53
Females	1	7	11	7	13	1	40
Total	5	11	29	20	23	5	93

Causes of Death.—Malignant disease, 23 patients; central nervous system disease, 23 (of whom 11 had cerebral infarction, and 7 cerebral or subarachnoid haemorrhage); cardiovascular disease, 19; subarachnoid disease, 9; gastro-intestinal disease, 9; trauma, 3; other causes, 7 (drug overdose 2, diabetic ketosis 2, renal failure 2, septicaemia 1).

Atheroma

The percentage frequency of the four atheroma grades (free, slight, moderate, and severe) in each arterial segment in men and women is shown in Table II. The highest incidence of severe atheroma is in the carotid sinuses, followed by the terminal carotid segments. The freedom from severe disease shown by the two intervening carotid segments (cervical and petrosal) is noteworthy. Not only does the grade of atheroma change sharply as the sinus gives way to the cervical segment but the type of lesion differs markedly also,

the sinus often being calcified and ulcerated, whereas the cervical segment rarely shows more than simple fatty streaking. The characteristic lesions found in the terminal carotid segment are calcified plaques. The vertebral artery in the majority of patients has only a small proportion of its surface area diseased.

There is no consistent difference in atheroma grading between the right and left sides, and between the sexes when the males as a group are compared with the females. If, however, men and women are compared on an age basis (Table III), there are more men than women with severe atheroma in the majority of sites in the age-groups 35–54 and 55–74 years. Over the age of 75, in many of the sites, the women have a higher incidence of severe atheroma than the men.

Stenosis

Distribution (Table II).—The highest incidence of stenosis is in the vertebral arteries, and it will be noted that one man in four in this unselected sample had severe vertebral narrowing. The high stenosis grade contrasts sharply with the low atheroma grade, and this is accounted for by the narrow calibre of the vertebral arteries, which allows them to be narrowed by the thick but localized fibrous plaques which are the characteristic lesions found in these vessels. After the vertebral arteries, the carotid sinuses are the most common sites for stenosis and were severely narrowed in one man in seven. Severe stenosis in other arterial segments is much less common, but its occurrence in a significant number of innominate, subclavian, and common carotid arteries should be remembered when angiographic investigation is undertaken. There is little difference between the right and left sides, but there is a consistent difference between the sexes, the females having a lower incidence of severe stenosis in every segment but one.

Site.—Many of the arteries have a characteristic distribution of stenosing lesions. Table IV shows the number of stenoses, both moderate and severe, which we found in the proximal, middle, and distal thirds of each artery. (Stenosing lesions in two or more thirds are classified as "multiple.") The innominate and subclavian arteries are commonly narrowed proximally; in the right common carotid artery distal stenosis is more frequent, while the left common carotid has a high incidence of narrowing proximally, in addition to a significant number of distal and multiple stenoses. The right vertebral narrowings are mainly single and proximal, whereas on the left multiple stenosis occurs

TABLE IV.—*Prevalence of Stenosis in the Different Parts of Each Artery, Expressed as the Number of Patients with Stenosis at Each Site. The Most Common Site of Stenosis in each Artery is Printed in Heavy Type*

Vessel	Number of Patients with Stenosis at Each Site				
	Thirds			Multiple	Total
	Proximal	Middle	Distal		
Innominate	**13**	1	0	0	14
R. common carotid	1	6	**13**	1	21
R. internal ,, sinus	—	—	—	—	32
R. ,, cervical carotid	0	0	**6**	0	6
R. ,, petrous ,,	1	3	**5**	1	10
R. ,, terminal ,,	0	7	**15**	10	32
R. subclavian	**33**	2	5	1	41
R. vertebral	**25**	4	2	8	39
L. common carotid	**11**	2	9	8	30
L. internal ,, sinus	—	—	—	—	40
L. ,, cervical carotid	1	1	**4**	2	8
L. ,, petrous ,,	0	3	**5**	2	10
L. ,, terminal ,,	2	10	**16**	10	38
L. subclavian	**13**	6	7	7	33
L. vertebral	14	3	2	14	33

TABLE II.—*Distribution of Atheroma and Stenosis in the Carotid and Vertebral Systems in Males and Females, Showing the Number of Patients with Each Grade in the Various Arterial Segments, Expressed as a Percentage of the Total Numbers of Male and Female Patients.*

System	Artery	Atheroma Grade								Stenosis Grade					
		Male				Female				Male			Female		
		O	Sl	M	S	O	Sl	M	S	O	M	S	O	M	S
Right carotid	Innominate	1	40	34	25	2	63	24	11	81	15	4	91	7	2
	R. common carotid	0	34	54	12	0	44	43	13	78	19	3	72	26	2
	R. carotid sinus	0	28	25	47	2	17	46	35	68	19	13	65	26	9
	R. cervical carotid	41	58	1	0	43	55	2	0	94	4	2	89	7	4
	R. petrous ,,	3	72	22	3	24	61	15	0	87	12	1	96	4	0
	R. terminal ,,	1	24	38	37	3	17	52	28	63	31	6	78	18	4
Right vertebral	R. subclavian	4	28	49	19	0	38	38	24	49	43	8	65	35	0
	R. vertebral	17	64	15	4	25	63	2	10	51	23	26	68	17	15
Left carotid	L. common carotid	0	29	59	12	0	48	41	11	60	31	9	78	15	7
	L. carotid sinus	0	24	29	47	0	9	48	43	59	26	15	54	37	9
	L. cervical carotid	35	63	1	1	43	55	2	0	87	9	4	98	2	0
	L. petrous ,,	5	67	25	3	4	85	11	0	88	10	2	94	4	2
	L. terminal ,,	0	28	38	34	0	22	43	35	54	44	2	74	26	0
Left vertebral	L. subclavian	13	25	43	19	5	40	25	30	62	32	6	68	30	2
	L. vertebral	14	63	19	4	30	58	5	7	62	11	27	68	20	12

Atheroma grades: O=Free. Sl=Slight. M=Moderate. S=Severe. Stenosis grades: O=No stenosis. M=Moderate. S=Severe.

TABLE III.—*Age-and-sex Distribution of Severe Atheroma Expressed as the Percentage of the Patients in Each Age-and-sex Group with Severe Atheroma in the Sites Specified.*

Age (Years)	Sex	Percentage of Patients in Each Age Group with Severe Atheroma													
		R. Carotid and Vertebral Systems								L. Carotid and Vertebral Systems					
		Innominate	Common Carotid	Sinus	Cervical	Petrous	Terminal	Subclavian	Vertebral	Common Carotid	Sinus	Cervical	Petrous	Terminal	Subclavian	Vertebral
35–54	Male	8	0	25	0	0	8	12	12	0	25	0	0	17	12	0
	Female	0	0	0	0	0	0	0	0	0	23	0	0	0	12	0
55–74	Male	23	15	54	0	3	33	16	3	15	56	3	5	31	19	6
	Female	9	24	29	0	0	24	22	6	10	29	0	0	29	28	6
75+	Male	41	12	47	0	6	65	29	0	12	41	0	0	53	21	0
	Female	19	6	62	0	0	50	36	21	19	69	0	0	63	43	15

as commonly as isolated proximal narrowing. The lesions in the tortuous petrous and terminal carotid segments are commonly found on the inner curvature of the bends.

Number of Systems Affected.—The brain receives its blood-supply through four systems: (*a*) right carotid system—innominate artery, right common carotid artery, carotid sinus and cervical, petrous, and terminal segments; (*b*) left carotid system—left common carotid artery, sinus, and so on; (*c*) and (*d*) vertebral systems, each consisting of the subclavian and vertebral arteries.

We have determined, for each of the 93 patients, the number of arterial systems which showed any degree of stenosis at any point along their course. We have also determined a second stenosis score for each of the 93 patients by assessing the number of systems which were severely narrowed. Thus a score of 0 in the graphs for all degrees of stenosis means that there was no narrowing at any point in any of the four systems. In the graphs showing severe stenosis, a score of 0 implies that none of the four systems had severe narrowing at any point along its course, and a score of 4 means that we had found a severe stenosis at some point in each of the four supply systems. Figs. 2, 3, and 4 show the age-and-sex distribution of these scores.

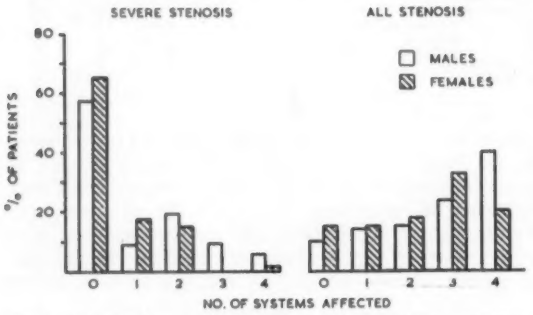

FIG. 2.—Distribution of the 53 males and 40 females according to the number of arterial systems affected by severe stenosis and by any degree of stenosis. Results expressed as a percentage of the patients of each sex studied.

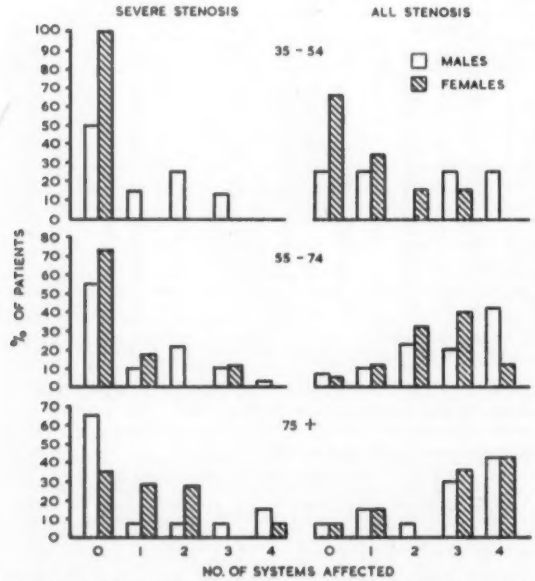

FIG. 3.—Age-and-sex distribution of patients, according to the number of arterial systems affected by severe stenosis and by any degree of stenosis. Results expressed as a percentage of the number of patients in each age-and-sex group.

The number of systems narrowed increases with age; in the patients under 75 the women have less stenosis, whereas in the age-group 75 and over the sex difference is abolished with respect to all grades of stenosis, and reversed for the patients with severe stenosis.

The high incidence of atheromatous stenosis in this unselected necropsy sample should be noted, for 90% of men and 85% of women have narrowing at some point along the four systems; and 43% of men and 35% of women have severe narrowing.

Correlation between Stenosis in the Carotid Sinuses and Vertebral Arteries.—In Table V we show the frequency with which patients with stenosis in one site are found to have stenosis in the other three sites; and Table VI shows the frequency of severe stenosis in patients with severe narrowing of the index vessel. It is clear that if a patient is found to have narrowing at one of these four sites there is a high probability that he has stenosis elsewhere. As the carotid arteries are more commonly investigated angiographically than the vertebral arteries, we have obtained further information on the correlation between the carotid sinuses by examining the vessels in 293 consecutive and unselected necropsies carried out on patients over the age of 35 (Table VII). Thus, if a carotid angiogram shows no stenosis of one sinus there is a probability of 81% that the opposite sinus will be free from stenosis. If one sinus is severely narrowed there is only a 19% chance that the other sinus will be normal.

TABLE V.—*Percentage of Patients With Stenosis of Index Artery Who Also have Stenosis in Other Sites*

Index Artery	% of Patients with Stenosis of Index Artery who have Stenosis in Other Sites			
	Other Sites			
	R. Sinus	L. Sinus	R. Vertebral	L. Vertebral
R. sinus	—	72	65	53
L. ,, ...	58	—	52	40
R. vertebral ..	46	54	—	62
L. ,, ...	51	48	73	—

TABLE VI.—*Percentage of Patients with Severe Stenosis of Index Artery Who Also have Severe Stenosis in Other Sites*

Index Artery	% of Patients with Severe Stenosis of Index Artery who have Severe Stenosis in Other Sites			
	Other Sites			
	R. Sinus	L. Sinus	R. Vertebral	L. Vertebral
R. sinus	—	50	60	60
L. ,, ...	45	—	55	90
R. vertebral ..	30	30	—	50
L. ,, ...	32	53	53	—

TABLE VII.—*Correlation Between Stenosis in the Carotid Sinuses. Data Drawn from 293 Unselected Necropsies, and Expressed as the Percentage of Patients with Various Grades of Stenosis in One Sinus Who have the Specified Grade of Stenosis in the Other Sinus*

Stenosis Grade Carotid Sinus	% of Patients with Stenosis of Carotid Sinus with Specified Grade of Stenosis in Opposite Sinus		
	Stenosis Grade—Opposite Sinus		
	None	Moderate	Severe
None	81	17	2
Moderate ..	52	39	9
Severe	19	28	53

Correlation Between Aortic Atheroma and Carotid and Vertebral Stenosis

Table VIII shows the percentage of the aortic area affected by complicated lesions and by all types of lesions in males with and without stenosis of the vertebral arteries and carotid sinuses. The age distribution of the patients with and without stenosis is similar, so that the differences in aortic disease are not simply a reflection of an age discrepancy. We have not attempted to compare the aortic atheroma in women, as the patients with stenosis are substantially older than the ones with no stenosis.

TABLE VIII.—*Relationship, in Males, Between Aortic Atheroma and Carotid and Vertebral Stenosis. Figures Represent Mean Values and their Standard Errors*

Group	% of Aortic Area Diseased	
	Complicated Lesions	All Lesions
No vertebral stenosis ..	7·9±1·8	37·7±3·3
Vertebral stenosis	14·8±3·0	43·2±3·4
P for difference	<0·05	<0·1
No carotid stenosis	7·8±1·4	36·3±2·7
Carotid stenosis	16·4±2·8	46·2±3·4
P for difference	<0·01	<0·03

Approximately twice as much of the aortic area is covered with complicated (ulcerated, calcified, and thrombotic) atheroma in males with narrowed vertebral arteries and carotid sinuses as in the men with no stenosis in these sites. The differences in the percentage of the aortic area covered by all types of lesions show a similar trend.

Atheromatous Ulceration

Atheromatous ulceration was found in 13 (10 men, 3 women) of the 93 patients examined (14%), and the lesions were often multiple. Ulcerated atheroma was found at some point along the carotid systems in 11% of the men and 2.5% of the women examined. The commonest single site was the sinus, and no ulcerated lesions were seen above this level. In the vertebral systems 7.5% of the men and 5% of the women had such lesions, which were all in the subclavian arteries. No ulceration of the vertebral arteries themselves was found.

It has been suggested that atheromatous ulcers might be a source of emboli and be thereby responsible for transient episodes of cerebral ischaemia, but there was no history of attacks of this type in any of our patients with ulcerating lesions.

Thrombotic Occlusion

Thrombotic occlusion of a neck artery was found in five patients (four male, one female), all of whom had cerebral infarction. Two of the occlusions were in the carotid systems and two in the vertebral; one patient had occlusion in both systems.

Correlation with Strokes

Of the 93 patients, 27 had had symptoms and signs indicating "cerebral vascular disease" (hemiparesis, or brain-stem manifestations). Fig. 5 shows the age-and-sex distribution of these patients as a percentage of the total number of patients in the sample in each age-and-sex group. Cerebral vascular symptoms are more common with increasing age, and it will be noted that a significant proportion of those patients over 75 with cerebral vascular symptoms had no stenosis in any part of the four systems studied, suggesting that there is some age-dependent factor in the causation of strokes which is not related to the state of the neck arteries. It will also be noted that the prevalence of strokes was greater in women than men in the under 75 age-groups, whereas at these ages we have shown that males have much more stenosis of the four supply systems than females.

In Figure 6 we have shown the number of systems narrowed in the 27 patients with strokes. Although 21 of these patients had narrowing of three or more systems, 10 of them were aged 75 and over, as opposed to one patient over 75 in the six patients with two systems or less narrowed. It should be noted that four of the 21 patients with three or more systems narrowed also had occluding thrombi.

If, as Fig. 5 suggests, the frequency of strokes rises with age even in patients with normal neck arteries, and

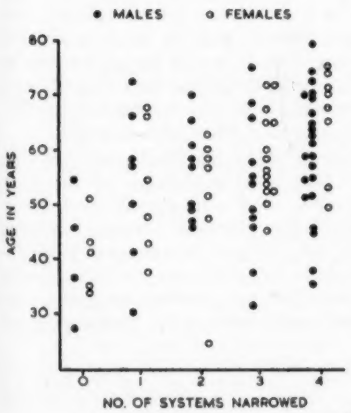

FIG. 4

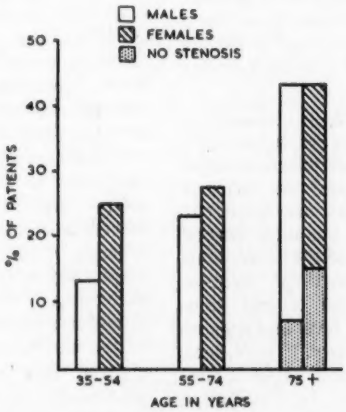

FIG. 5

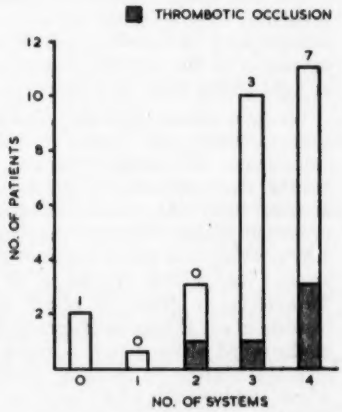

FIG. 6

FIG. 4.—The number of arterial systems with any degree of stenosis, plotted against the age of the patient, for each of the 93 patients studied. FIG. 5.—Age-and-sex distribution of the 27 patients with cerebral vascular disease, expressed as a percentage of the total number of patients studied in each age-and-sex group. The stippled area denotes those patients with cerebral vascular disease who had no stenosis of any of the four arterial systems. FIG. 6.—Distribution of the 27 patients with cerebral vascular disease according to the number of arterial systems with any degree of stenosis. The figures above each block show the number of patients in that group aged 75 or more, and the hatched areas represent patients with complete thrombotic occlusion of a neck artery in addition to atheromatous stenosis.

as the frequency of narrowing of the neck artery increases with age, strokes and neck-artery narrowing would show a strong correlation even if the disease of the neck artery is not causally related to the strokes.

Discussion

One of the most striking features of atheroma of the carotid and vertebral systems is its patchy distribution. Some arteries, and indeed some sites within an arterial segment, have a high incidence of lesions, whereas other areas are virtually free from disease. The contrast between the carotid sinus and the cervical carotid artery immediately distal to it is the most outstanding example, and this difference has been noted in other studies (Keele, 1933; Fisher, 1954; Samuel, 1956). The high incidence of proximal lesions in the innominate, subclavian, vertebral, and left common carotid arteries is also a significant finding and contrasts with the right common carotid artery where lesions are most commonly found in the distal third. The higher frequency of atheroma and stenosis in the terminal part of the carotid system than in the cervical and petrosal segments should also be remembered when any explanation of this patchy distribution is considered.

The localization of lesions might be determined by the structure of the vessels or by their response to the fluid under pressure that is flowing through them. There is no consistent difference in structure, using conventional microscopical and histological techniques, between sites with a high and a low atheroma prevalence. Thus, the carotid sinus is a thin-walled elastic vessel, the cervical portion is a predominantly muscular artery, and the terminal segment is a very-thin-walled muscular vessel; but we cannot detect any structural difference between the proximal and distal segments of arteries such as the common carotid, which have marked discrepancies in atheroma frequency. Dynamic factors consequent on blood flowing under pulsatile pressure through the system might be of significance by producing local areas of turbulence and by increasing the strain on the vessel walls. Stehbens (1959) made glass models of arteries and studied the turbulence which these systems produced when water flowed through them. He found that it was more likely to develop in an S-bend, simulating the terminal carotid segment, than in a straight tube like the cervical segment, and it readily developed in the proximal segment of a branch arising at right angles from its parent trunk.

We have shown that the vessels which come off at approximately right angles from another artery (the innominate, left common carotid, and left subclavian arteries from the arch of the aorta, and the vertebral arteries from the subclavian trunks) are prone to proximal lesions, whereas the right common carotid artery, which is a direct continuation of the innominate artery, has a low incidence of proximal stenosis. Turbulence is likely to occur in the carotid sinus because of the change in calibre at this level and because of the origin of the external carotid artery. There does, therefore, appear to be some correlation between sites where turbulence is likely to occur and the distribution of atheroma, but even if Stehbens's findings apply to resilient tubes perfused in a pulsatile manner with a fluid whose flow properties differ from those of water the way in which turbulence contributes to atheroma is unknown. The part played by distortion of the neck vessels by movement of the cervical spine and by osteophytes due to cervical osteoarthritis is also uncertain.

We have found that there is a definite sex-difference in atheroma and stenosis when men and women of similar age are compared, this difference in atheroma being obscured when the men as a group are compared with all the women. The sex-difference is abolished and in some respects reversed in the patients over 75, but this may not reflect the true natural history of the disease, for it may be that the men with severe atheroma have died at an earlier age, leaving a highly selected group of older survivors.

The relationship between neck-artery stenosis and the development of strokes remains, in our view, uncertain. Hutchinson and Yates (1957) selected 83 patients with cerebral vascular symptoms and found that 40 (48%) had significant narrowing of one or more of the four supply systems. Their criterion for narrowing was reduction of the lumen to less than half, which is the same standard that we have used for our severe stenosis grade, so that the results of the two studies may be compared (Table IX). Of our 93 unselected patients, 37 (40%) had one or more systems severely narrowed, and this proportion does not differ significantly from Hutchinson and Yates's 48%, although the patients were selected in completely different ways. Of our 37 patients with severe narrowing of one or more systems, 18 had strokes, but their mean age is higher than that of the patients without stenosis, and five of them had occluding thrombi in addition to stenosis. We feel that neck-artery occlusion is directly related to cerebral vascular symptoms, and, as Hutchinson and Yates's stenosis grade embraced thrombotic occlusion also, it would be of interest to know how the 22 patients whom they found with cerebral infarcts were distributed between two subgroups—stenosis alone and stenosis plus occlusion.

TABLE IX.—*Comparison Between Present Study and that of Hutchinson and Yates* (1957)

Series	Number of Patients with No Stenosis of Neck Systems and with One or More System Narrowed	
	No. of Systems Narrowed	
	None	One or More
Hutchinson and Yates (1957) ..	43 (52%)	40 (48%)
Cerebral vascular symptoms ..	43	40
Present study (severe grade of stenosis)	56 (60%)	37 (40%)
Cerebral vascular symptoms ..	9	18
Thrombotic occlusion	0	5
Mean age	62 years	70 years

If one accepts that the prevalence of strokes rises with age, even in the absence of narrowing of the neck artery (Fig. 5), and as the amount of neck-artery atheroma and stenosis also increases with age, studying a group of patients with strokes at necropsy or angiographically would give a high incidence of neck-artery narrowing. However, without further evidence, one should not necessarily conclude that the stroke is caused by the narrowing.

From the practical viewpoint, we feel that the relationship between stenosis in the four systems should be noted. Thus if a patient is found to have a narrowing in one system there is a very high probability that the other systems will show stenosis. The occurrence of a significant number of severe stenoses at sites not commonly displayed by angiograms—the proximal parts of the innominate, subclavian, and left common carotid arteries—should also be remembered.

Summary

The age-and-sex distribution of atheroma and stenosis of the carotid and vertebral systems in 93 unselected necropsies is described. Attention is drawn to the frequency with which lesions occur in some sites, and possible reasons for this are discussed.

The relationship between neck-artery stenosis and aortic atheroma, and also the strong correlation between stenosis in the four neck artery systems, are described.

The relationship between strokes and neck-artery stenosis, ulceration, and occlusion, is discussed.

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ACUTE MYXOEDEMA PRECIPITATED BY PNEUMONIA

REPORT OF FIVE CASES

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It seems to be generally unknown that myxoedema may have a sudden onset in seemingly healthy individuals. Search of the literature has not produced any well-substantiated cases. Watney and Douthwaite (1932) described the case of a woman of 63 whose first symptoms of myxoedema began in December and who was almost in myxoedema coma when seen by them the following February. Lloyd (1933) reported the case of a woman aged 55 who was said to have been in perfect health in August, but when seen by him in October presented a typical picture of myxoedema. Means (1948), quoting these two cases, comments: "Our guess is that these cases were not actually more acute than others, but that the apparent acute onset was the final blossoming of a picture which must have been present, although unnoticed, for a longer period." Asher (1955) states: "Myxoedema is a chronic rather than acute disease, and therefore rarely presents with a crisis. It only does so when the disease has progressed to a very advanced stage, or if an acute complication develops."

In the past two years we have jointly observed three cases of severe myxoedema of very rapid onset, apparently precipitated by pneumonia, and two similar cases were previously seen by one of us (W.H.). One of these cases has been reported in a different context (Le Marquand, Hausmann, and Hemsted, 1953). We are concerned, therefore, with five patients who appear to have developed acute myxoedema as a result of pneumonia.

Case 1

A man aged 60 was well and working until three days before his admission to hospital, when he became confused and lethargic. He had no cough or pyrexia. His doctor detected an area of dullness in the left chest, swelling of the face and neck, and suspected carcinoma of the lung with cerebral metastases and mediastinal obstruction. On admission (February 25, 1959) he was pale and myxoedematous in appearance. His mental reactions were slow and he had marked oedema of the face and legs. *X*-ray examination of the chest showed enlargement of the heart and left-upper-lobe consolidation, which a few days later spread to the right lower lobe. An electrocardiogram showed low voltage of QRS in standard leads and inversion of T waves in leads I, aVL, V_3, and V_5. Radioiodine uptake test gave very low normal values verging on mild hypothyroidism. Serum cholesterol was 295–365 mg./100 ml.

He was treated with penicillin, streptomycin, and thyroxine and slowly lost his extensive oedema, though some of the myxoedematous appearance remained. Cardiographic tracings returned to normal after three weeks' administration of thyroxine, on which he has since been maintained in good health. A follow-up chest film showed a heart of normal size and complete clearing of both lung fields.

Comment.—In this case acute myxoedema was provoked by pneumonia which, though clinically and radiologically extensive, was practically symptomless.

Case 2

A woman aged 52 gave a week's history of right-sided pain in the chest with productive cough and slight pyrexia. For the previous two years she had been tired and received iron tablets for anaemia from her own doctor. Her husband was admitted to hospital five days earlier with severe pneumonia. On admission (April 11, 1959) her appearance was clearly myxoedematous. Speech and reactions were slowed down and there was marked oedema of the face and legs. The temperature was 99.4° F. (37.4° C.) and she had physical signs of extensive right-upper-lobe pneumonia. *X*-ray examination of the chest showed an enlarged heart with consolidation of the posterior segment of the right upper and right middle lobes; further films suggested fluid at the right base. Serum cholesterol was 380 mg./100 ml. and haemoglobin 71%. The electrocardiogram showed bradycardia, low voltage, and T-wave inversion consistent with myxoedema. Radioiodine uptake test showed "low normal thyroid activity; thyroid leg ratio consistent with hypothyroidism."

She was treated with penicillin, streptomycin, thyroxine, and chlorothiazide, and made a very slow recovery. Eight weeks later her lung fields were radiologically clear and the size of the heart was reduced, but cardiographic tracings still showed low voltage. After three months her heart was of normal size, the electrocardiogram normal, and haemoglobin 90%. Since then she has remained in very good health on a maintenance dose of thyroxine.

Comment.—This patient had few systemic symptoms and low pyrexia in spite of very extensive pneumonia. Her two years' history of lassitude and anaemia suggests the possibility of pre-existing mild hypothyroidism, with sudden deterioration under the stress of severe pneumonia.

Case 3

A woman aged 76 was admitted to hospital on December 20, 1955, in a semicomatose condition. Reaction to

questioning was exceedingly slow, movements were ponderous, her voice was husky and appearance myxoedematous. The pulse rate was 70 a minute, rectal temperature 95° F. (35° C.), blood-pressure 95/50 mm. Hg, thyroid not palpable. There was an area of dullness with bronchial breathing and coarse crepitations at the left base. *X*-ray examination of the chest revealed consolidation of the basal segments of the left lower lobe and some shadowing at the right base. An electrocardiogram showed bradycardia with low voltage and inverted T waves, compatible with myxoedema. The haemoglobin was 65%.

She was treated with penicillin, streptomycin, and thyroxine and made good progress. A further chest film one week later showed that the lung fields were nearly clear. She was discharged on January 17, 1956, with a haemoglobin of 80%, but was readmitted half-conscious on March 7, again following respiratory infection. She was finally discharged on a maintenance dose of thyroxine.

Comment.—In this case no reliable previous history could be obtained, but a woman aged 76, living alone, may be assumed to have been reasonably well to be able to cope with her household duties.

Case 4

This patient was a woman aged 73. We cannot do better than quote from her doctor's letter: "I have seen quite a lot of her recently while attending her husband for lobar pneumonia. She is normally pretty alert and active. When calling to see her husband to-day I was told that she had been weak and drowsy for the past two days. She spoke slowly in a deep voice and seemed confused. There was considerable oedema of the legs and around her eyes. A few hours ago she apparently had some sort of fit and was unconscious, pale, and foaming at the mouth. This lasted about 15 minutes, during which time she bit her tongue but was not incontinent. I saw her shortly afterwards, when she was pale and semicomatose. She has now improved and is rational, but speaks very slowly and in a deep voice. There is no previous history of any illness or fits, nor of any nervous trouble. Her heart sounds are of poor quality and the rate is 50 a minute. I think this must be a case of acute myxoedema."

On admission to hospital on January 22, 1958, she was comatose; the temperature was 80° F. (26.7° C.), pulse rate 56, and blood-pressure 145/80. She died 12 hours later in spite of treatment. A necropsy report (Dr. F. Hampson) stated: "The thyroid was small and appeared rather fibrosed on cut section. There was much greenish pus in the trachea and main bronchi, and beads of pus could be expressed from the cut surfaces of both lungs." The cause of death was certified as myxoedema coma.

Comment.—This is a case of outstanding interest. The patient here was actually observed by her doctor while acute myxoedema developed over a period of 48 hours. The evidence that pneumonia was the precipitating cause seems very strong: she was nursing her husband, who was suffering from pneumonia, and post-mortem findings were suggestive of bronchopneumonia or purulent bronchitis. Another striking point was the observation of an epileptic fit preceding the onset of coma; this course of events has been noted in other cases of myxoedema coma, where it usually indicated rapid deterioration and death.

Case 5

A woman aged 61, whose case has been previously reported (Le Marquand *et al.*, 1953), was admitted to hospital on January 7, 1951. She had had two episodes of left hemiplegia, in both cases followed by rapid recovery, and was in good health until two weeks before admission, when she developed a cold and a severe cough. When first seen by her doctor the day before admission she was confused. Marked oedema of the face and eyelids developed in the next 24 hours. She died after four days. At necropsy extensive right-sided pneumonia and fibrosis of the thyroid gland were found.

Discussion

Myxoedema of rapid onset has, so far as we know, never been reported. This is in marked contrast to other endocrine deficiency states, such as diabetes mellitus, Addison's disease, and hypopituitarism, which often present with acute crises. Physiological reasons may account for this discrepancy, and observations after thyroidectomy have shown that there is usually an interval of one to two months before myxoedema becomes apparent. The most convincing evidence to this effect was reported by Gilligan *et al.* (1934), who studied 47 patients after total removal of the normal thyroid gland because of intractable heart disease or angina pectoris. They state: "After varying periods of time some of the signs and symptoms of myxoedema developed in every patient following total thyroidectomy. By the end of the first post-operative month most of the patients showed mild clinical signs and symptoms, such as dry skin, slight pallor, and sensitivity to cold. After the second post-operative month more serious symptoms of myxoedema developed in many patients, such as weakness of the extremities, drowsiness, muscle irregularity, and transient puffiness of the face, hands, and feet." It should be noted, however, that in all these cases normally functioning glands were removed, and that the position may be quite different if thyroidectomy were carried out when the thyroid was already defective.

It is our hypothesis that in the five cases reported by us the thyroid gland was already considerably damaged, and that the residue of functioning thyroid tissue was working under maximum stimulation from the thyrotropic hormone. There was therefore no clinical hypothyroidism prior to the onset of the acute illness (with the possible exception of Case 2), but these patients had no reserve when exposed to severe stress. We believe that this is the probable explanation of the course of events as observed by us.

The most important stress factor in all our cases was pneumonia, which involved more than one lobe in four of our patients, while in the fifth (Case 4), who was nursing her husband with pneumonia until two days before the onset of her illness, there was post-mortem evidence of purulent bronchitis. Another stress factor was exposure to cold; four of our cases occurred during the winter months, the fifth in early April. Inquiries have shown that the first 10 days of April, 1959, were exceptionally cold compared with the previous two years, that humidity was unusually high from April 4 to 10, and that notifications of pneumonia during the first half of April were higher than usual.

We have no evidence that pneumonia as a stress factor stands in any specific relation to the thyroid gland and that other stresses may not lead to similar results, but we feel that, in this country at least, pneumonia and exposure to cold are the two major influences.

It is true to say that as none of these patients was investigated prior to admission the evidence for the acuteness of the onset of myxoedema is not conclusive; it is certainly very strong in Case 4, where the patient was actually observed by her doctor while myxoedema developed over a period of 48 hours. It is also strong in Cases 1 and 5, where the patients were thought to be quite normal before the onset of pneumonia. Of the

remaining two cases all we can say is that thyroid function, perhaps already inadequate in Case 2, deteriorated acutely with the onset of infection, while in Case 3 no previous history was available but the patient became rapidly comatose with the development of pneumonia.

A final point of interest was the contrast between the relative lack of symptoms and the evidence of extensive consolidation in four of our five patients. We think that the silent character of these severe infections is a matter of significance which needs stressing, and that attention should be drawn towards the possible presence of myxoedema when faced with pneumonia with minimal symptoms.

Summary

Five cases of myxoedema of acute onset, including one new case of coma, are reported. The stress factors were severe pneumonia and exposure to cold. It is suggested that in all these cases there was a sudden breakdown of function in potentially inadequate thyroid glands, already working at maximum capacity to meet normal requirements. As the pneumonia caused few symptoms in all our patients it was liable to be overlooked.

We thank Dr. E. Hughes, Medical Officer of Health for Reading; for help with the meteorological data; Dr. F. Hampson and the staff of the pathological laboratory for their reports; Dr. W. G. Evans and Dr. D. V. Mabbs for the radioiodine studies; and Dr. G. L. T. M. Patey for permission to quote from his letter.

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The Second British Congress on the History of Medicine and Pharmacy was held in London from September 27 to 29. It was organized by the Faculty of the History of Medicine and Pharmacy of the Worshipful Society of Apothecaries of London with the co-operation of the Chemical Society. The subject chosen for discussion was "Chemistry in the Service of Medicine," and papers were read at the Apothecaries' Hall, at the Royal College of Physicians, at the Royal College of Surgeons, and at the Chemical Society, Burlington House. At a brief ceremony during the Congress the chairman of the Faculty, Dr. W. S. C. Copeman, conferred the Faculty's honorary fellowship on Professor K. J. Franklin, F.R.S., distinguished physiologist and medical historian, and on Dr. Ernst Wickersheimer, president of the Société Internationale d'Histoire de la Médecine and a leading historian of medicine in France. During the Congress a dinner was held in the hall of the Worshipful Society of Apothecaries. The guest of honour was Sir Howard Florey, P.R.S., and the president of the Chemical Society, Sir Alexander Todd, F.R.S., gave an address. Sir Alexander discussed the long-standing relation between chemistry and medicine, and stressed that medicine and the search for health had provided a great stimulus to chemical research. He foresaw the day when the accepted separation of the basic sciences would have to be broken down. At present the range of skills for tackling a research problem comprehensively could probably only be found in research institutes, but research could best be carried out in the universities, which must use the constant influx of young minds to cross the barriers between the sciences.

NUCLEAR SEXING WITH ACETO-ORCEIN

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Nuclear sexing, which stems from the discovery of sexual dimorphism in interphase nuclei (Barr and Bertram, 1949), is now accepted as a routine clinical diagnostic test (Lennox, 1956; Davidson, 1960). The oral-mucosal-smear method (Moore and Barr, 1955; Marberger, Boccabella, and Nelson, 1955; Klinger and Ludwig, 1957) has gained wide popularity because specimens may be obtained with minimal inconvenience to the patient. The present paper describes the application of the aceto-orcein squash technique to oral mucosal smears. It is just as accurate as other methods but much more rapid, and it has the additional advantage that fine details of nuclear structure are more readily revealed by squashing and flattening the freshly obtained cells.

Materials and Methods

Stains

Orcein may be used with or without lactic acid.

Stock Solution.—Synthetic orcein, 1 g.; glacial acetic acid, 45 ml. Boil, cool, and filter.

Simple Aceto-orcein.—Dilute 45 parts stock solution with 55 parts distilled water and filter. Periodic filtration is necessary.

Lacto-aceto-orcein.—Dilute 50 parts stock solution with 50 parts of 70% lactic acid and filter.

Fresh Preparations

An oral mucosal smear is obtained by scraping the inside of the patient's cheek with a wooden spatula. Several short vertical strokes are made with firm pressure, and the desquamated cells and saliva are then scooped up on the end of the spatula and spread on the surface of a clean dry slide. One drop of stain is quickly placed on the centre of the smear and a thin coverglass —$\frac{1}{8}$ in. (22 mm.) square or $\frac{1}{8}$ by $1\frac{1}{2}$ in. (22 by 38 mm.) rectangle—is laid over it. One or more layers of filter paper are placed on top and the coverglass is pressed down by drawing the thumb across from one end of the slide to the other. To avoid moving the coverglass on the slide the filter paper is firmly held down over one corner of the cover with the left hand while the right hand moves across from left to right. The filter paper absorbs excess stain expressed from below the coverslip. With insufficient pressure the nuclear membrane is wrinkled: with correct pressure the nuclei are evenly flattened. Extrusion of the nuclei from the cell is not disadvantageous provided that the nuclear membrane remains intact. With simple aceto-orcein they should be stored in a covered tray in a refrigerator and fresh stain added to the edge of the coverglass to prevent drying out. The hygroscopic lactic acid in lacto-aceto-orcein

prevents drying out, and experience has shown that the slides may be kept at room temperature for as long as six weeks.

Scrutiny

Simple aceto-orcein stains the nucleus and cytoplasm more rapidly than lacto-aceto-orcein, but temporary preparations of either type may be scrutinized immediately. With both stains, contaminating bacteria are not prominent at first but become more obtrusive with prolonged staining. Although other methods may give preparations in which bacteria are relatively unobtrusive there is considerable loss of cells in processing. With orcein, however, there is an abundance of cells from which to select ideal nuclei. The orcein smear can be readily scanned with a 1/7-in. oil-immersion objective, which gives a large field and depth of focus. An optical glass filter of peacock blue (Type OB2), which is complementary in colour to orcein red, is advantageous.

Permanent Preparations

To make permanent preparations the slides are inverted in a ridged dish in a 3 : 1 mixture of absolute alcohol and glacial acetic acid until the covers separate. As cells adhere to the cover and slide both are given three two-minute washes in absolute alcohol, cleared in "euparol essence," mounted in "euparol," either separately or recombined, and left on a warm plate to dry. Pretreatment with silicone prevents adhesion of cells to coverslip but precludes immediate scrutiny of the temporary preparation with an immersion lens, since the silicone on the upper surface of the cover prevents even spreading of the immersion oil.

Surveys

A small survey of normal subjects was carried out in a mixed class of over 100 students. Oral mucosal smears were obtained, aceto-orcein preparations were made on coded slides, and scrutiny of each was carried out without knowledge of the sex of the subject.

A larger survey of all the inmates in an institution for oligophrenic mental defectives was carried out. The material was collected in a few hours by a team of two, one obtaining the smears and the other making the preparations. In one group of 100 subjects who were lined up for examination the smears were obtained and the preparations made at a rate of more than 20 every five minutes, the slides and coverslips having been cleaned and numbered beforehand. In the oligophrenic subjects contamination with bacteria and food particles or other debris was a frequent cause of unsatisfactory smears, and about 20% of the preparations had to be repeated. The nuclear sex was recorded as chromatin-negative if no structure resembling sex chromatin was seen in 30 consecutive suitable nuclei. In preparations with sex chromatin present a minimum of 30 consecutive nuclei with sex chromatin were scrutinized. The nuclear sex was recorded as chromatin-positive if there was no suggestion of multiple sex chromatin bodies in any of these nuclei. In smears where a proportion of the nuclei showed more than one body (chromatin-double-positive), or in doubtful or difficult smears, new preparations were obtained, and in these at least 100 suitable nuclei were scrutinized.

Results

Normal Subjects

In every case sex was diagnosed correctly. With simple aceto-orcein, staining of the sex-chromatin body is so extremely rapid that a smear may be obtained, stained, and photographed all in less than a minute. Sex chromatin is seen with equal clarity in permanent preparations. In obtaining oral mucosal smears it was found necessary to exert firm pressure to secure suitable cells, for patches of cells with different types of nuclei occur. The patches are apparently derived from three different epithelial strata. (1) The superficial layer contains pyknotic degenerating nuclei which are often heavily contaminated by bacteria. (2) The intermediate layer provides nuclei suitable for sexing. These have a smooth nuclear membrane and finely granular nucleoplasm in which the sex-chromatin body, if present, is deeply stained. (3) The deep layer has nuclei with prophasic chromosomes and prominent nucleoli.

Oligophrenic Subjects

Preparations from 245 apparent males were scrutinized. Two smears were found to be chromatin-positive and 243 were chromatin-negative. Both subjects with chromatin-positive nuclei were found to have the typical clinical and hormonal feature of medullary dysgenesis (Stewart *et al.*, 1959). Smears from 240 apparent females were scutinized. One subject was found to have double-positive nuclei and was apparently an example of the triplo-X syndrome (Stewart and Sanderson, 1960). Smears from the other 239 female subjects were chromatin-positive and none was chromatin-negative.

Nuclear Morphology

Orcein-stained nuclei exhibit fine details of nuclear morphology. A chromatin-negative nucleus (Fig. 1) has a finely granular nucleoplasm and a well-defined nuclear membrane with no sex chromatin. A chromatin-positive nucleus (Fig. 2) is similar but exhibits sex chromatin adjacent to the nuclear membrane. In some nuclei from normal females the sex-chromatin body is

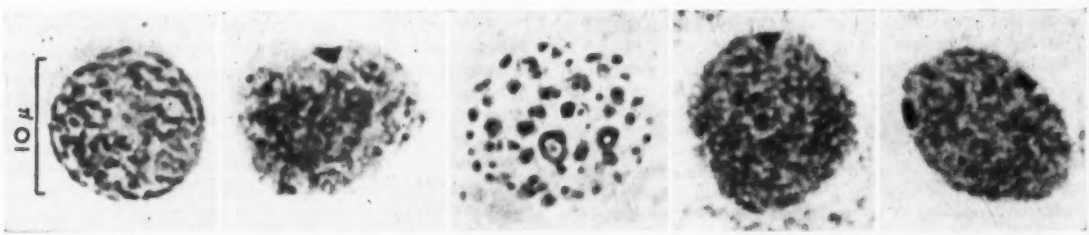

Fig. 1 Fig. 2 Fig. 3 Fig. 4 Fig. 5

Fig. 1.—Typical chromatin-negative nucleus from a normal male. Fig. 2.—Typical chromatin-positive nucleus from a normal female. Fig. 3.—Degenerating nucleus unsuitable for sexing. Fig. 4.—Chromatin-positive nucleus from a male with medullary dysgenesis. Fig. 5.—Chromatin-double-positive nucleus from a triplo-X female.

apparently connected to a nucleolus by a fine chromatin thread. The sex-chromatin body may appear flattened, convex, tent-shaped, or diplococcoid at the nuclear membrane. It may also lie in the centre of the nucleus, but it cannot always be distinguished from a nucleolus, and such centrally placed chromatin bodies are therefore not suitable for enumeration. Nuclei which are unsuitable for sexing include those which are pyknotic and degenerating (Fig. 3), crumpled and crenated, or contaminated by bacteria, although these may be eliminated by careful focusing.

In males with medullary dysgenesis and chromatin-positive nuclei (Fig. 4) the sex chromatin body is exactly comparable to that found in a normal female. In the triplo-X female some nuclei have two such chromatin bodies (Fig. 5). These are positioned at random on the nuclear membrane, opposite, adjacent, or closely adjacent to each other. In some chromatin-negative nuclei derived from normal (XY) males a slim heterochromatic crescent is discernible at the nuclear membrane. A similar structure is present together with sex chromatin in some chromatin-positive nuclei derived from male subjects with medullary dysgenesis (XXY) but apparently absent from nuclei derived from normal (XX) or from triplo-X (XXX) females.

Discussion

Orcein has several advantages for nuclear sexing. These include ease of preparation, rapidity of sexing, and the revelation of fine details of nuclear structure.

Ease of Preparation and Rapidity of Sexing.—Orcein preparations may be made with extreme ease and rapidity, and scrutiny is facilitated by squashing, which enlarges the nuclei. Simple aceto-orcein is better for rapid sexing since it stains so very quickly. Lacto-aceto-orcein is recommended for survey work, as temporary preparations may be made with great facility at the rate of 250 an hour but may be scrutinized at leisure because they do not deteriorate for several weeks. The value of the technique for survey work has been demonstrated by our results, which are consistent with recent large surveys of male (Barr *et al.*, 1959) and female (Fraser *et al.*, 1960) oligophrenic patients. Our results also provide some additional data of value in establishing the incidence of sex-chromosome anomalies in such populations.

Revelation of Fine Detail.—Squashing of the nucleus, with subsequent enlargement, permits study of its fine structure. The fine chromatin thread which apparently connects the sex-chromatin body to a nucleolus was first recognized by Reitalu (1957) in foetal tissue, and was subsequently described by Serr and his co-workers (Serr *et al.*, 1958; Lennox *et al.*, 1960) in tissue-culture material. In view of the difficulties of sexing encountered in foetal tissue (Park, 1957) and in tissue culture (Miles, 1960) the recognition of this structure in oral mucosal smears is of value. The importance of this structure with respect to the nature of sex chromatin is discussed elsewhere (Stewart, 1961). The discovery of a slim heterochromatic crescent in male nuclei stained by orcein (Sanderson, 1960) has been confirmed by other workers (Ohno and Makino, 1961). Evidence is as yet insufficient to correlate it with heterochromatin derived from the Y chromosome, although this is the most likely explanation of its presence in males (XY and XXY) and its absence in females (XX and XXX).

Summary

The sex-chromatin body is readily recognizable in oral mucosal smears stained with orcein. Simple aceto-orcein is recommended for rapid nuclear sexing, and lacto-aceto-orcein is recommended for survey work. In a survey of 245 males and 240 females in an institution for oligophrenic mental defectives two cases of medullary dysgenesis and one triplo-X female were found.

The aceto-orcein method reveals fine details of intranuclear structure, including a structure found in the nuclei of subjects with a Y chromosome and perhaps related to heterochromatin derived from this chromosome.

We are indebted to Dr. M. M. Macrae, physician-superintendent, Strathmartine Hospital, Dundee, for permission to investigate patients under his care and for facilities associated with the survey. We are indebted also to Mr. J. Scott, of the Natural History Department, for technical assistance.

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Medical Memoranda

Traumatic Rupture of the Heart

Rupture of the heart after myocardial infarction has long been recognized as a dramatic and rapidly fatal complication. The incidence of rupture of the ventricle subsequent to acute myocardial infarction is given as between 1 and 10% of the post-mortem cases of myocardial infarction (Kohn, 1959).

A rather less common cause of rupture of the heart is that following trauma to the body, in which the chest wall or pericardium remains intact (Crane, 1952). The diagnosis of this condition is difficult, as the following case report shows. After trauma to the body, in which the chest wall or pericardium remains intact, rupture of the healthy myocardium can only conceivably occur as a result of profound changes in intrathoracic and intracardiac pressure.

Cardiac trauma produced by contusive and concussive forces may lead to disruption of the cardiac musculature (Bright and Beck, 1935). Cardiac tamponade, with an ultimately fatal issue, will occur after a varying lapse of time (Pollock *et al.*, 1952). Recovery may occur after

traumatic infarction of the heart (Anderson, 1940). The successful suture of a ruptured myocardium after non-penetrating injuries has been carried out (Desforges *et al.*, 1955).

Case Report

A married woman aged 46 was admitted to hospital at 3.25 p.m. on April 10, 1960. She was driving a motor-car, and in a collision her chest had been crushed against the steering-wheel. She had been unconscious prior to admission, but when admitted was conscious though mentally confused. Her blood-pressure was 40/? mm. Hg and a noradrenaline infusion (4 ml. to 1 pint (570 mL) of saline) was started at once. Whole blood was given as soon as it was available. The patient was very restless and there was some bruising of the anterior and the right side of her chest wall. The abdomen showed no rigidity or rebound tenderness, but guarding was present below both costal margins. The heart sounds were soft but clearly heard. Air entry was good into both lungs. *X*-ray examination of the chest revealed fractures of the fifth to the eighth ribs on the left side. There was no haemothorax. No fracture of the skull was noted on *x*-ray. It was felt that the cause of peripheral circulatory failure was rupture of some abdominal organ or haemorrhage from the liver. She was not considered fit for operation, and blood transfusions were continued.

At 10 p.m. the patient was mentally improved; she remembered the accident, and inquired after passengers. The next morning her blood-pressure was maintained at 80/60 mm. Hg and the pulse was 120. Breathing was laboured, but air entry was good on both sides. *X*-ray examination of her chest revealed a small collection of fluid at the right base and a right interlobar fissure. There were vigorous bowel sounds. An E.C.G. taken showed (*a*) sinus tachycardia of 140 beats a minute, (*b*) right axis deviation, (*c*) low voltage. These signs did not indicate any specific lesion, and there was nothing to suggest cardiac tamponade. In the afternoon the patient was seen by a thoracic surgeon, who felt that there was no haemopericardium or traumatic myocarditis. He thought that the condition was due to rupture of the liver and advised further blood replacement.

At 3 a.m. on April 12 the patient clutched at her abdomen, drew up her legs and became very restless. On examination her blood-pressure was 80/60 and pulse 120. The abdomen was very tender and rigidity was present, especially in the upper half. She had had 6 pints (3.4 litres) of whole blood and 2 pints (1,140 ml.) of normal saline. It was felt that a laparotomy should be carried out immediately.

Premedication with atropine 0.6 mg. was given. The patient received 200 mg. of thiopentone and 30 mg. of tubocurarine. A cuffed orotracheal tube was passed and anaesthesia was by nitrous oxide and oxygen. Breathing was maintained by intermittent positive-pressure ventilation. Whole blood was given continuously throughout the operation. Laparotomy revealed a small amount of bile-stained fluid in the peritoneal cavity. The pancreas was contused, but no obvious rupture was found in any organ. The liver was enlarged and engorged. During the operation the patient's condition deteriorated, the blood-pressure being unrecordable, and peripheral cyanosis occurred in spite of vigorous inflation of the lungs with pure oxygen. The patient improved after the administration of 10 mg. of methoxamine, and this was later repeated. Atropine 0.6 mg. and neostigmine 2.5 mg. were given and spontaneous breathing started. On leaving the theatre the blood-pressure was 90/50, but the patient remained cyanosed in spite of being placed in an oxygen tent. She died about 15 minutes after returning to the ward.

Post-mortem Report

The body was that of a well-nourished young middle-aged woman showing abrasions over both knees and some bruising to the front of the chest. There were no other external signs of injury.

Thorax.—Two pints (1,140 ml.) of blood-stained fluid were found in each pleural cavity. There were some old adhesions over the right lung and fractures of ribs two to eight inclusive on the left side and front. *Heart.*—The pericardial cavity contained ¾ pint (425 ml.) of blood. The heart was normal in size; extensive bruising of the whole of its outer surface and a small rupture of the heart at the tip of the right ventricle were present. The valves and chambers were otherwise normal and the coronary arteries showed no atheroma. The muscle was a good colour. *Lungs.*—Both lungs were collapsed and showed acute congestion with acute oedema. *Abdomen.*—A midline abdominal operation had been done recently, and there was also an old midline abdominal operation scar. No free fluid or adhesions were seen. A drainage-tube had been present. *Liver.*—This was a little enlarged and flattened, extending down rather farther than normal into the abdominal cavity. There was some surface bruising in the subcostal region, but no evidence of deep bruising of the liver or lacerations. On section the organ showed chronic venous congestion. *Pancreas.*—There was a little bruising but no evidence of any external generalized pancreatitis. *Skull.*—Some bruising to the top of the scalp had occurred, but there was no evidence of fracture. *Brain.*—The cerebral arteries showed no atheroma. There were no abnormalities of the brain on the surface or on section apart from one area of bruising of the cortex 1 in. (2.5 cm.) in diameter situated over the left frontal lobe.

Cause of Death.—Death was due to extensive bruising, with a small rupture of the heart and bruising of the abdomen caused by recent pressure injuries to the front of the chest and abdomen.

Comment

The problems of diagnosing traumatic rupture of the heart when the chest wall remains intact were obvious in this case. This patient presented with internal haemorrhage and there were no signs to indicate traumatic myocarditis. She was overtransfused, and this may have been a contributory cause of death. In the light of the clinical findings it was believed that she was suffering from hypovolaemic circulatory failure, and that intravenous therapy with whole blood was the only way of saving her life.

With the increasing number of accidents on the roads, especially deceleration accidents in which the chest wall is injured by the steering-wheel of the car, traumatic rupture of the heart must be borne in mind.

Thanks are due to Mr. G. J. Walley for permission to publish this case, and to Dr. E. H. Seward for his valuable criticism and encouragement.

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The Walter and Eliza Hall Institute, in Melbourne, has received a grant of $164,000 from the United States Department of Health. The money is to be used for the purchase of equipment to further research into what body cells do to protect themselves against disease, including cancer and the common cold. The work is being carried out by Dr. Gustav Nossal, who for the past two years has been working at Stanford University, California, under Professor Joshua Lederberg, who had earlier worked with him in Melbourne.

Reviews

PHARMACOLOGY AND THERAPEUTICS

Pharmacology. The Nature, Action and Use of Drugs. By Harry Beckman, M.D. Second edition. (Pp. 805+xvii. £5 8s. 6d.) Philadelphia and London: W. B. Saunders Company. 1961.

This large and handsome volume—a remarkable tribute to the erudition of its sole author—is prefaced by the intimidating statement that it is "a textbook for the undergraduate medical student, who can devote but a fleeting moment in his career to prepare for the pharmacologic aspects of the practice which lies ahead." As it has taken the reviewer many hours to sample, even in the most cursory fashion, its admirable contents, it must be concluded that "the fleeting moment" which the medical student is expected to devote to pharmacology is a relative term. Further, each of the many chapters in the book is fully documented by scores of well-chosen references. It would take, one would think, aeons of time to read them all, but the author states that "the bibliographies are not exhaustive and only meant to serve as guides for excursions into the literature." The preface therefore leaves one with an overwhelming sense of inadequacy and a deep admiration for the industry of the modern medical students of Milwaukee.

The work is divided into three sections. In the first pharmacology is briefly orientated to other preclinical disciplines; in the second a broad background is presented of the science of pharmacology with an exposition of the bases from which advances have been made; in the third, which comprises the major part of the text, the actions and uses of drugs are discussed. The book is written in a conversational—almost chatty—American style, with a frequent use of the first person which is usually distasteful to a British reader but in this case is curiously pleasing.

It is definitely a textbook of applied pharmacology rather than one of the pure academic science, and differs from many others in that in most chapters it attempts a synthesis of the subject and does not confine itself to the pharmacological actions and uses of this or that drug. Thus in the chapter on anaesthetics it is recognized that a skilled anaesthetist uses many agents to produce analgesia, muscular relaxation, the blocking of reflexes, and sleep, and a balanced account of the whole process is presented, rather than a single description of the pharmacological actions and uses of a variety of anaesthetic agents with little or no reference to each other.

Lastly, the work is obviously written not only by a skilled pharmacologist but by one who is also an experienced clinician. In this it again differs from most other textbooks of pharmacology, which, though they may be excellent when dealing with the science, are apt to be disappointing when they wander into the field of therapeutics. It would be difficult to find fault with the therapeutic advice given in this volume, which is up to date, practical, and full of common sense. This is indeed a very good book.

DERRICK DUNLOP.

INTERSEXUALITY

Die Intersexualität. Edited by Dr. Claus Overzier. (Pp. 560 +xv; illustrated. DM. 119.) Stuttgart: Georg Thieme Verlag. 1961.

This is an outstanding volume on a subject of much topical interest, and is written and produced according to the best tradition of the German monograph. As is pointed out in the foreword, the phenomenon of intersexuality, of atypical sexual development, has been known for many thousands of years, but has only recently changed from being a mere curiosity to becoming a fascinating focal point of both clinical and scientific interest, one indeed which is being probed by the most modern techniques of hormone analyses, nuclear sexing, and chromosomal analyses. This work deals with all these modern developments with great thoroughness. As an example of this, the chapter on hormones and intersex ends with a list of 389 references and the title of every paper is given in full. The chapter on true hermaphrodites includes a detailed analysis of 146 cases from the literature, and concludes with 238 references to such cases. The whole work is thoroughly up to date and it maintains throughout a broad international outlook on the literature. It consists of 20 sections by various authors. These include three contributed by well-known British authorities, one by an American pair, and one from Canada. Five further sections are written by Professor Dr. C. Overzier, the general editor. One problem in a book by many contributors is that of maintaining an equally high standard throughout, but this has been very well achieved in this volume.

For those English-speaking medical men who read German with difficulty, and who feel that the effort of reading a foreign text is only to be justified by subject matter of exceptional quality, it may be said that this is one of the books which well reward such effort. It is valuable for its very complete text, for its many references, and not least for its many beautifully clear illustrations and diagrams and its tables relating to many subjects.

This is likely to prove a main work of reference on its subject. It should be in all medical libraries, and will be needed by all active workers in fields both clinical and scientific which impinge in any way on the problems of disordered human sexual development.

C. L. COPE.

SMOKING

Smoking. Its Influence on the Individual and Its Role in Social Medicine. By C. van Proosdij. With a Foreword by Richard Doll. (Pp. 319+viii. 57s. 6d.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1960.

The effect of smoking on health has become one of the most important problems in preventive medicine today. Here we have a habit which is undoubtedly responsible for at least three-quarters of the steadily increasing number of deaths from lung cancer, and for an important but less easily definable proportion of the morbidity and mortality from chronic bronchitis; and which probably makes a contribution to the morbidity and mortality of ischaemic heart disease and of pulmonary tuberculosis in older men. It is within the power of every individual to decide whether he will adopt or continue this habit which has such profound effects on

health and longevity. Yet in spite of official statements affirming these ill effects, albeit rather less emphatically than the seriousness of the situation appears to warrant, the amount of tobacco consumed, chiefly and increasingly in the most dangerous form as cigarettes, actually increases slowly. There is clearly here a failure of communication in the field of health education. Since it appears useless to rely upon Government action in this important matter, possibly because of the heavy financial interest which most governments have in the continued consumption of tobacco, a heavy responsibility rests on medical men to make the best contribution they can to the enlightenment of the public and to the counteraction of the unavoidable propaganda in favour of smoking to which the public and especially the young are persistently exposed. To this end all medical men should be well informed on all aspects of smoking, its history, its pharmacology and psychology, its effects in predisposing to and aggravating disease, and its social aspects. Dr. van Proosdij's book attempts to provide this information within reasonable compass and on the whole it succeeds well. The literature on the many aspects of the smoking problem has attained proportions unmanageable by the busy doctor. Dr. van Proosdij summarizes it ably and fairly, and provides a good balanced survey of the subject.

Perhaps the least satisfactory section is that (fortunately brief) dealing with possible substitutes for tobacco. Few would regard tobacco as comparable in its socio-psychological aspects with cocaine, hashish, opium, or sleeping drugs which are seriously discussed as possible substitutes. And the experience of the many ex-smokers who have given up smoking without needing to adopt any substitute shows that it is unnecessary and indeed unwise to suggest that a substitute is needed. In spite of such minor criticisms the book can be recommended to anyone seeking reliable information on the smoking problem; the excellent and well-arranged bibliography will be of great value to those wishing to consult original sources.

J. G. SCADDING.

SURGERY OF PORTAL HYPERTENSION

The Surgical Treatment of Portal Hypertension, Bleeding Esophageal Varices and Ascites. By M. Judson Mackby, M.D., D.A.B.S., F.I.C.S. With a Foreword by Emile Holman, M.D. (Pp. 250+xviii; illustrated. 84s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

This is a short book which contains a great deal of useful information. It is well produced and well illustrated. It is pleasant to read and impresses on first acquaintance. According to the author it is "intended to be primarily a manual of practical management," yet much of the book is strangely at variance with this purpose. It omits entirely the clinical aspects of the diseases causing portal hypertension. Not a single venogram is illustrated; and though two and a half pages are devoted to the technique of splenoportography no mention is made of its inaccuracies or risks, nor is the alternative method of direct portal venography so much as suggested.

Much of the technical instruction is good, though far too much emphasis is placed on ineffective and obsolete methods. For example, two full pages are devoted to hepatic arterial ligature though it is considered to be "only of theoretical and historical interest." The operation of "portal-azygos bisection" is briefly described, but Tanner's name is not mentioned. Removal of the gall-bladder is advocated in doing a porta-caval anastomosis. Almost all of the current practice in the treatment of portal hypertension is listed, but without authority. Presumably this is because the hospital experience on which the book is based is no more than 22 shunt operations done in cases selected from among 334 cirrhotic patients studied at the Kaiser-Permenente Hospital. The book does not give the impression that the experience of operations other than shunts is any less brief. As a supplement, a chapter on current nation-wide (U.S.A.) practice is wisely added, though it hardly does credit to the numerous and distinguished contributors whose views are condensed into fourteen somewhat idiomatic pages.

Lists of references are given at the end of each chapter; these and many more are re-listed at the end of the book and the names are again given in the index, where they often refer only to the bibliography. The source of the author's information is thus given in bulk and often many times over, yet specific acknowledgment is rarely made in the text. Even more surprising is that twelve of the names referred to in the historical review beginning on page 59 are not listed at the end of the chapter, and five of these important references are not given anywhere in the book. The impression is thus left that text and bibliography were drawn up independently. A brief calculation shows that, in a book of 250 pages, only 132 are of text and illustration. The cost is £4 4s.

ALAN H. HUNT.

FREUD AND AFTER

Freud and the Post-Freudians. By J. A. C. Brown. (Pp. 225 +viii. 3s. 6d.) London: Penguin Books. 1961.

Psycho-analytic theory has undergone considerable changes since it was first evolved. Some of them have been changes of emphasis, while others have been more fundamental. Psycho-analysis has also contributed to new psychological theories of neurotic behaviour. It has become almost impossible for the psychiatrist and psychologist not specializing in this field to follow these developments. They will find this book very helpful. Its author is a social psychiatrist familiar with academic psychology and psycho-dynamics. He surveys critically the present state of psycho-analytic theory and its contributions to psychology, medicine, and sociology, and he outlines the more important theories which derived from psycho-analysis, beginning with Jung and Adler and including Klein, Sullivan, Horney, and Fromm. While the majority of the post-Freudians discarded the biological foundations of psycho-analytical theory, the Kleinian approach, according to the author, emphasizes biological factors in behaviour to a degree which makes environmental influences almost unimportant. He believes consideration of social factors to be perfectly compatible with Freud's theory, which he regards as the greatest single advance in the understanding of human personality so far conceived. He advocates its widest possible application in psycho-therapy and social science. He sees a real danger in psychiatrists turning away from psychological methods to the indiscriminate use of drugs. This lively and well-written book deserves to be read by students of human behaviour whatever their theoretical bias may be.

E. STENGEL.

THOREK'S CHASTENER

Surgical Errors and Safeguards. By Max Thorek, M.D., LL.D., Sc.D., F.I.C.S., F.B.C.S., F.P.C.S.(Hon.), D.C.M., F.R.S.M. Fifth edition. (Pp. 652+xvi; illustrated. £10.) London: Pitman Medical Publishing Co., Ltd. 1961.

In previous reviews of the first (1932) and fourth (1945) editions of this well-known book a very favourable opinion of its value was expressed. After a long interval the fifth edition has been published following the much regretted death of its world-famous author last year, and as his son, Philip Thorek, explains in the preface the tremendous advances in surgical practice in the intervening years have made it necessary for the whole book to be completely rewritten and for sections to be undertaken by some 22 collaborating authors. While this was probably inevitable we cannot help feeling that the book has thereby lost many of the very experienced and acceptable opinions of its originator.

One extensive new section of some 65 pages concerns cardiac surgery, and very properly deals only with the safeguards in the handling of such cases. It is copiously illustrated with clear diagrams of the various lesions, electrocardiograms, and radiographs. Incidentally, the diagrams on p. 309 purporting to illustrate a mitral commissurotomy actually show an aortic operation. In view of this emphasis on cardiac surgery it is surprising that there is no reference—except for a brief mention of coronary replacement—to the newer work on vascular surgery which from the point of view of the community is much more important. In the rather short section on thoracic surgery we noted the statement "To R. Nissen (1931) belongs the credit of the first lobectomy," but as long ago as 1900 Glück performed lobectomies upon two septic cases successfully.

On the whole, however, the volume is very informative, well illustrated and produced. As we stated in an earlier review, it can be relied upon to have a chastening effect upon the too ardent novice, which was the author's aim.

The various editions of this work make an interesting commentary upon the increasing costs of book production, for whereas the original 1932 edition of 691 pages cost 45s. the fourth edition of 1,085 pages in 1945 cost 90s., while the present edition of 652 pages works out at 200s.

NORMAN C. LAKE.

Current scientific research and hypotheses are often well presented to the laymen, but a recent book is among the best of its kind. In *Science Survey 2*, edited by A. W. Haslett and John St. John, 23 working scientists discuss a variety of topics in a clear and authoritative way. On the biological side there are chapters on transmission of nerve impulses, the working of muscle cells, psychological and chemical studies of the mind, and the measurement of noise. The chapters on physics include several of interest on the structure and formation of the earth. The volume is published by Vista Books, London (pp. 372, 30s.).

A second edition of the well-known manual *Occupational First Aid* has been issued by the St. John Ambulance Association. It includes a new section on minor dressings. The book should be regarded as a supplement to the ordinary first-aid manuals. The emphasis is mainly on occupational hazards in factories, but it would be found helpful to first-aiders in some other types of occupation. It is obtainable (4s. 6d.) from the St. John Ambulance Association, Stores Department, St. John's Gate, London E.C.1.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Medicine in Tropical Africa. A Realistic Approach. By Michael Gelfand, C.B.E., M.D., F.R.C.P., D.P.H., D.M.R. (Pp. 243; illustrated. 30s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Surgery of Trauma in the Tropics. By R. L. Batten, B.A. (Cantab.), F.R.C.S. With a chapter on anaesthetics by J. V. Farman, M.B., B.S.(Lond.), F.F.A. R.C.S. (Pp. 234+viii; illustrated. 35s.) London: Edward Arnold. 1961.

Oral Exfoliative Cytology. Interim Report of Veterans Administration Co-operative Study. (Pp. 74+vi; illustrated. $1.50.) Washington: Veterans Administration. 1961.

Saliva and its Relation to Oral Health. A Survey of the Literature. Compiled by D. Afonsky, L.D.S., D.D.S., Ph.D. (Pp. 785+xxiv. $12.) University of Alabama Press. 1961.

Mining Town Doctor. By Peter Kennedy. (Pp. 191. 16s.) London: Peter Davies. 1961.

The Operation. By Leonard Engel. (Pp. 224. 2s. 6d.) London: Pan Books Ltd. 1961.

Looking Over My Shoulder. By C. Willett Cunnington. (Pp. 208; illustrated. 25s.) London: Faber and Faber. 1961.

The Nurse and her World. A Young Person's Guide. By Pamela Bright. (Pp. 144. 9s. 6d.) London: Gollancz. 1961.

The Patient's Attitude to Nursing Care. By Anne McGhee, A.M.I.A. (Pp. 94+viii. 10s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Night Calls. A Study in General Practice. By Max B. Clyne, M.D., with an additional chapter by Aaron Lask, M.A., M.R.C.S., D.P.M. (Pp. 216+xvi. 21s.) London: Tavistock Publications. 1961.

Essays on the First Hundred Years of Anaesthesia. Vol. II. By W. Stanley Sykes, M.B.E., M.B., B.Chir.(Cantab.), D.A. (Pp. 187+viii; illustrated. 30s.) Edinburgh and London: E. and S. Livingstone Ltd. 1961.

Nutritive and Therapeutic Value of Fruit and Vegetables. Food and Agriculture Documentation Series, No. 31. (Pp. 148. 9s.) European Productivity Agency. Organization for European Economic Co-operation. Available from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

Cells and Cell Structure. By E. H. Mercer, D.Sc., Ph.D. (Pp. 100; illustrated. 12s. 6d.) London: Hutchinson Educational Ltd. 1961.

Subtraktion. By Professor Dr. B. G. Ziedses des Plantes. (Pp. 71; illustrated. DM. 28.) Stuttgart: Georg Thieme Verlag. 1961.

Mentally Subnormal Spastics. Addresses given at a Conference held in London, December 1960. (Pp. 30; illustrated. 4s. 6d.) London: British Council for the Welfare of Spastics. 1961.

Motiv und Schuld. Eine psychiatrische Studie über den Handlungsaufbau bei kriminellen Verhalten. By Friedrich Stumpfl. (Pp. 75. Sch. 73.) Vienna: Verlag Franz Deuticke. 1961.

Fellowship Examination Papers for the Diplomas of the Royal College of Surgeons, Edinburgh, 1956-1961. (Pp. 55. 5s. 6d.) Edinburgh: E. and S. Livingstone Ltd. 1961.

I Tumori Primitivi del Palato. By Pietro Miani and Lorenzo Marcucci. (Pp. 228; illustrated. No price.) Parma: Edizioni "L'Ateneo Parmense." 1960.

Actualités Néphrologiques de l'Hôpital Necker, 1961. Introduction by Professor J. Hamburger. (Pp. 312; illustrated. NF. 58.50.) Paris: Éditions Médicales Flammarion. 1961.

Measurements in Medicine. Some Epidemiological Contributions to the Etiology and Control of Infection. By Robert Cruickshank, M.D., F.R.C.P., D.P.H. (Pp. 44. No price.) Edinburgh: Royal College of Physicians. 1961.

Anaemia and Operations on the Gastrointestinal Tract. By Sir Stanley Davidson, B.A., M.D., M.D.(Oslo), F.R.C.P.(Edin.), F.R.C.P.(Lond.), F.R.S.Ed. (Pp. 44. No price.) Edinburgh: Royal College of Physicians. 1961.

Mary and Caroline and the Lay Contribution to Preventive Medicine. By C. W. Dixon. (Pp. 14. No price.) Dunedin: University of Otago Press. 1961.

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ORAL POLIOMYELITIS VACCINE

A leading article earlier this year[1] discussed the possibility of replacing in Britain the Salk inactivated poliomyelitis vaccine by the Sabin attenuated oral vaccine, not merely to counteract an epidemic but for general immunization. It was considered in view of the evidence from the extensive vaccination campaigns involving many millions of persons that the Sabin oral vaccine is a safe and effective prophylactic. The Sabin vaccine has a great advantage in being administered by mouth instead of by repeated injections and consequently is more acceptable to the public. But the decision to change from Salk to Sabin vaccine must rest mainly on their relative immunizing qualities, and here there is a fundamental difference in their action. Whereas the Salk vaccine may reduce the incidence of poliomyelitis it can do little to eliminate the polioviruses from the gastro-intestinal tract of man. Oral vaccination on the other hand can produce not only an antibody immunity but also resistance of the gut to infection. Thus when given on a mass scale, which is practicable with oral vaccine, it can eliminate the polioviruses from the population.

These opinions are now supported by the Public Health Laboratory Service in their report to the Medical Research Council, published in the opening pages of the *Journal* this week. The report gives the results of a trial of Sabin vaccine administered to infants in various parts of Great Britain. It accepts the safety of the Sabin vaccine and stresses the ease with which it can be administered. The report also points out that the vaccine confers a gut immunity in addition to stimulating the production of antibodies, and draws attention to the feasibility of vaccinating virtually the entire population, thus ensuring an immunity of the herd as well as of the individual. These views should encourage the Ministry of Health to change over as soon as possible from Salk to Sabin vaccine for general immunization.

This year has not been an entirely happy one in Britain with regard to the incidence of poliomyelitis in spite of the fact that Salk vaccination has been going on since the spring of 1956. There is no question that the Salk vaccine has been effective in protecting many of those who have received it, mainly persons under 15 years of age, but the scale on which it has been given has not been sufficient to cover a high enough proportion of the susceptible population in order to ensure the immunity of the herd. Since the Sabin vaccine is now being commercially produced in Britain it is possible to give the vaccine to whole communities regardless of whether or not individuals have had Salk vaccine.

In the Public Health Laboratory Service's trial a comparison based on production of antibody and on virus colonization in the gut was made of the effectiveness of three different immunizing schemes. Three groups of infants between 6 and 12 months of age with more than 100 in each group took part. One group received a single dose of trivalent vaccine containing all three types of poliovirus, the second group three doses of trivalent vaccine at four-week intervals, and the third group three doses of monovalent vaccine at four-week intervals in the order type 1, type 3, and type 2. Each dose of virus contained one million virus particles as determined by tissue-culture infection. Incidentally it is not clear why this dose was chosen, since most workers have used, with satisfactory results, doses of the order of one hundred thousand virus particles. However, the results showed that one dose of trivalent vaccine was not satisfactory but that good results were obtained with both the three doses of trivalent and the three doses of monovalent vaccine; in fact there was little to choose between these two schemes. On the grounds of simplicity and ease of administration the Public Health Laboratory Service strongly recommends the scheme comprising three doses of trivalent vaccine. On this scheme only one vaccine would be necessary, which would certainly make recording less complicated. The scheme could easily replace the Salk-vaccine scheme in the general immunization schedules recently published by the Ministry of Health[2] and furthermore it is probably the best scheme for those vaccinees who do not turn up for the second or the third dose.

It would also seem advisable, though the report makes no mention of this, to use the trivalent vaccine when attempting to counteract an epidemic by mass vaccination of the community at risk. This was done successfully in Tashkent in 1959[3] during an epidemic of type-1 virus. Although in such an emergency a vaccine containing one type of virus—namely, that of the epidemic strain—would be somewhat more effective in dealing with the epidemic, the use of the trivalent vaccine is less complicated because it can be followed up by the second and third doses, thus

[1] *Brit. med. J.*, 1961, 2, 293.
[2] Ibid., 1961, 2, 763.
[3] Chumakov, M. P., *et al.*, *Bull. Wld Hlth Org.*, 1961, 25, 79.
[4] Poliomyelitis Research Foundation, *S. Afr. med. J.*, 1961, 35, 253.

completing the immunization course and ensuring immunity to all three types of poliovirus.

It is therefore difficult to understand why the Ministry of Health in combating the present outbreak of type-1 poliomyelitis at Hull is using Sabin vaccine containing only type-2 virus. Such a vaccine will confer only a relatively limited degree of protection against the epidemic strain, mainly by interference (namely, by preventing the colonization of the gut by the epidemic virus), and will leave the population still at risk to future infection with type-1 virus. In adopting this policy the Ministry may wish to avoid being placed in the invidious position of explaining that a case of poliomyelitis which might coincidentally follow vaccination cannot possibly be due to the vaccine virus. But surely this is unnecessary. By now, after the enormous scale on which the Sabin vaccine has been used, the stage must have been reached when its safety is no longer in doubt. In March of this year the Poliomyelitis Research Foundation at Johannesburg[4] drew attention to the fact that: "It has not yet been proved that one single case of paralytic poliomyelitis has been caused by the administration of Sabin strains in vaccinees or their contacts, and the number of vaccinations now probably exceed 90 million." The time would therefore seem to be ripe for a more realistic attitude in dealing with poliomyelitis outbreaks by using a vaccine containing the epidemic type.

The conclusion was recently expressed in these columns[1] that oral poliomyelitis vaccine offers the greatest possibility of completely eliminating poliovirus as a human pathogen provided proper safeguards are taken in its manufacture and careful surveillance of the community is maintained. It is of the utmost importance for the vaccine to be used in a correct manner so as to obtain the best protection either when combating an epidemic or when providing general immunization. The report from the Public Health Laboratory Service has given an excellent lead, and it deserves careful study.

CHEMOTHERAPY OF TUBERCULOSIS IN INDIA

Although tuberculosis is a less alarming disease than it once was, it is not always realized that even in economically developed countries the improvement in tuberculosis statistics is very much more in mortality than in morbidity. In less developed countries the disease still remains a grave problem. In some places active infectious pulmonary tuberculosis afflicts as many as one in twenty of the adult population, and in most Asiatic countries surveyed the prevalence varies between 0.5 and 5%. Many of these countries lack funds, equipment, and trained staff to treat and prevent a disease which is causing vast misery and economic loss. It is no use trying to transfer European or North American methods directly to Asiatic or African countries: they are neither economically nor socially feasible.

A few years ago, in an effort to develop new techniques appropriate to India and similar countries, a Tuberculosis Chemotherapy Centre was founded in Madras.[1] This imaginative and far-sighted enterprise is a remarkable example of international co-operation. It is jointly sponsored by the Indian Council of Medical Research, the Madras State Government, the World Health Organization, and the British Medical Research Council, whose Tuberculosis Research Unit is responsible for the scientific planning. Within a few years it has produced results of great importance not only for India but for every country in which tuberculosis is not under control.

The first question the centre set out to answer was whether, under Indian conditions, patients with pulmonary tuberculosis could be treated as effectively at home as in a sanatorium or hospital. If this proved possible the government could clearly be spared the immense cost of providing beds and would be able to spend its limited funds to better effect. Patients with newly diagnosed pulmonary tuberculosis, mostly far-advanced, were allotted at random to a group treated for one year with P.A.S. and isoniazid in a sanatorium or to a group given the same chemotherapy at home. At the end of one year it was found that those treated at home had fared as well as those treated in the sanatorium, in spite of the fact that the patients treated at home lived in slums, had much less food and rest, and had in fact taken less of their drugs than the patients in hospital.

A recent report[2] relates the progress in the second and third years of patients from both groups who achieved bacteriological quiescence at the end of the first year of chemotherapy. In the second year these patients were allotted at random to two groups, one receiving treatment with isoniazid alone and the other with a placebo. In the third year half of the isoniazid group who remained quiescent continued with the drug. All the other quiescent cases received a placebo. In the second and third years all patients were treated at home.

Of the 61 patients who received one year of chemotherapy, 6 relapsed in the subsequent two years, (two with isoniazid-resistant organisms) compared

[1] Tuberculosis Chemotherapy Centre, *Bull. Wld Hlth Org.*, 1959, 21, 51.
[2] Devadatta, S., *et al.*, ibid., 1961, 24, 149.
[3] Andrews, R. H., *et al.*, ibid., 1960, 23, 463.
[4] Ramakrishnan, C. V., *et al.*, ibid., 1961, 24, 129.
[5] Mitchison, D. A. *et al.*, *Tubercle (Lond.)*, 1960, 41, 1.
[6] Tuberculosis Chemotherapy Centre, *Bull Wld Hlth Org.*, 1960, 23, 535.
[7] Fox, W., *Tubercle (Lond.)*, 1958, 39, 269.
[8] Velu, S., *et al.*, *Bull. Wld Hlth Org.*, 1960, 23, 511.

with three relapses in the 65 patients who had two or three years of chemotherapy. Two of the three had resistant organisms and the third had taken isoniazid very irregularly. All except one of the relapses occurred in the second year. The bacteriological relapse rate of patients with residual cavitation was only slightly greater than of those without. Relapse was a little commoner in those with initially more extensive disease and more strongly positive sputum.

On the whole the relapses were effectively treated by further chemotherapy. At the end of the third year, of the 130 patients who had quiescent disease after one year's treatment only two had active disease: one of these had been persistently uncooperative and the second seemed on the point of becoming quiescent. Two other patients had died, but neither directly from tuberculosis.

Two other reports[3 4] examine the effect on their contacts of treating at home patients with such strongly positive sputum. It was found that after the initial diagnosis and start of treatment the incidence of later tuberculin-conversion and active tuberculosis among the contacts of those treated entirely at home was no greater than among the contacts of those removed to a sanatorium for the first year of treatment. Presumably chemotherapy had very rapidly reduced the infectiousness of the index case.

These results are very encouraging. They have shown that even under the poorest social conditions chemotherapy can give as good results in the home as in a sanatorium or hospital, and without any additional risk to the contacts. But the conditions under which out-patient treatment was carried out were not typical: the work was done by a large, highly trained, well-equipped, and devoted team who could afford the time to obtain the confidence of their patients and their patients' families and to supervise them closely. It would certainly be cheaper to provide such teams in developing countries than to provide and staff large numbers of sanatorium beds but it would not necessarily be easier. Devoted, enthusiastic, and well-informed leaders are the first essential. These are not easy to come by where doctors and leaders are at a premium.

There are further problems to solve, but we now at least know that in developing countries out-patient treatment should be the general rule, for when carried out in the best possible manner it can be as effective as treatment in hospital. The chemotherapy used in these trials—oral P.A.S. and isoniazid initially, followed in certain groups by isoniazid alone—was less than ideal. The failure rate in the first year was about 10%. It has still to be determined whether more expensive chemotherapy, with a lower failure rate or none, might not in the end save money. Better initial treatment should greatly reduce the necessity of treating failures with very expensive second-line drugs and the spread of resistant tubercle bacilli in the community. This is controversial; but what is clear is that in many developing countries valuable foreign currencies are used on drugs which are then so mishandled by uninformed practitioners, qualified or unqualified, that drug-resistant tubercle bacilli are produced and disseminated to an alarming extent. If this is allowed to continue tuberculosis will become much more difficult and expensive to control, if indeed it can be controlled at all.

Meantime all the governments and agencies concerned deserve high praise for the success of the Madras experiment. For the work outlined above is by no means all that has been done. It has been shown, for instance, that Indian strains of tubercle bacilli differ from European in pathogenicity.[5] The prevalence and significance of primary drug-resistance has been investigated.[1 6] Much work has been done on the problem of self-medication at home.[1 2 6–8] And to all this research the highest scientific standards have been applied. But perhaps the most remarkable achievment of the Madras team is to have followed up all patients now for more than three years.

CAUSES OF GLAUCOMA

In health fluid traverses the eye at all times in a continuous flow. It enters from the region of the ciliary body, circulates within the globe, and passes through the pupil to the anterior chamber. It gains exit via the trabecular meshwork in the angle to reach the canal of Schlemm and thence the extraocular venous system. In primary glaucoma affecting the adult there is an obstruction to this flow, but it may operate by either of two distinct mechanisms.

Closed-angle glaucoma affects the small hypermetropic eye, wherein the lens is relatively large and bulky. The lens continues to grow throughout life and by the age of 50 years it may act as a bung in the pupil aperture. The intraocular pressure rises in the posterior chamber behind this obstruction and the iris is billowed forward like a sail before the wind. The aqueous in front of the iris flows out of the globe; the anterior chamber, which is already shallow, becomes shallower still, and the peripheral part of the iris is forced against the trabecular meshwork on the inner side of the canal of Schlemm. Thus flow becomes impossible. The intraocular

pressure rises rapidly and the cornea becomes oedematous and hazy, so that the patient experiences blurring of vision and may see coloured haloes round lights. In the first attacks the obstruction is often relieved by sleep, when the pupil becomes small, the angle reopens, and the normal flow is restored. Repeated attacks may permanently damage the trabecular meshwork, so that flow becomes partially reduced and the intraocular pressure is permanently raised.

In glaucoma simplex the flow is gradually reduced, despite an open angle, by a different mechanism, which is at present ill understood. The site of the obstruction is probably in the trabecular meshwork itself, which becomes gradually less permeable with advancing age. The earliest clinical indication of this process is an increased lability of intraocular pressure in its diurnal variation and a reduction of outflow as measured by tonography. Unfortunately the eye is symptomless during this early phase, and diagnosis of glaucoma simplex depends on the ophthalmologist's inspired suspicion. Routine tonometry after the age of 40 has been advocated, and has proved to be of value in discovering early cases.[1] Recently the knowledge that heredity plays a considerable part in the causation of glaucoma simplex has been exploited in early diagnosis by the measurement of outflow in siblings[2] and offsprings[3] of affected patients.

The obstruction to outflow is progressive, and eventually in both types of glaucoma the intraocular pressure is permanently raised. The globe gives way at its weakest point (the optic-nerve head), to produce pathological cupping of the disk. The nerve fibres of the retina are compressed at the margin of the disk and further embarrassed by ischaemia, so that groups of these fibres cease to function, producing characteristic field defects known as arcuate scotomata from their arching configuration round the fixation point. The scotomata enlarge if the pressure is not relieved, and the whole field of vision is finally engulfed.

The firm recognition of the two varieties of glaucoma has gradually become established over the last twenty years, though acceptance of this classification has been slow. This is a reflection of the fact that when diagnosed late the two types of glaucoma present a similar clinical picture. Recently J. D. Abrams[4] has analysed 1,861 consecutive cases of glaucoma attending the Institute of Ophthalmology, London, and the findings suggest that mixed glaucoma, wherein both types of pathological lesion exist, is rare. Forty-seven subjects with this possible diagnosis were studied in detail and only three genuine cases of mixed glaucoma were found.

The early diagnosis of closed-angle glaucoma depends on a careful history, and a lead may be given by the presence of a shallow anterior chamber and a narrow angle. Provocation tests should follow, entailing the measurement of outflow after exposure to darkness,[5] when a dilated pupil prevents easy outflow of the aqueous through a narrow angle. Glaucoma simplex, which is the main cause of blindness in this group of diseases, still defies early recognition because of the symptomless phase during the early stages. A positive family history in antecedents is a most valuable clue to diagnosis before the optic nerve head is injured, and all patients, especially over the age of 40 years, with a history of glaucoma in their family owe it to themselves to disclose this fact when they undergo a routine eye test. The examiner in turn must ensure that in such subjects the early signs of simple glaucoma are sought by the use of the tonometer and, where possible, by an assessment of outflow.

[1] Reed, H., and Bendor-Samuel, J. E., *Trans. ophthal. Soc. U.K.*, 1957, 77, 379.
[2] Paterson, G., ibid., 1961, in press.
[3] Miller S. J. H., ibid., 1961, in press.
[4] Abrams, J. D., *Brit. J. Ophthal.*, 1961, 45, 503.
[5] Foulds, W. S., ibid., 1959, 43, 613.

CARPAL-TUNNEL SYNDROME

The correspondence columns of this journal bear witness to the continuing interest in the carpal-tunnel syndrome. It is an important but not the only cause of acroparaesthesia. The cardinal symptoms[1] are nocturnal paraesthesia of intense burning quality confined to the thumb, index, and middle finger, and occurring in middle-aged women, particularly after a day of active hand exercise (knitting, sewing, washing). Objective sensory change may be found in the median nerve's territory in the fingers (but rarely in the palm of the hand). Weakness of opponens pollicis and abductor pollicis brevis with wasting of the lateral border of the thenar eminence may precede, but usually follows, the sensory symptoms.

The diagnosis may be difficult when objective changes are absent and the patient is uncertain about the distribution of paraesthesia. Most patients at first insist that all fingers are affected, and agree that the little finger is spared only after a period of observation directed to this point. The differential diagnosis from cervical spondylosis, thoracic-inlet syndrome, polyneuritis, subacute combined degeneration, and rarely disseminated sclerosis may not be easy. The minority of cases presenting as thenar wasting may suggest early motor-neurone disease. The inexperienced may be

[1] Garland, H., Bradshaw, J. P. P., and Clark, J. M. P., *Brit. med. J.*, 1957, 1, 730.
[2] Kendall, D., ibid., 1960, 2, 1633.
[3] Heathfield, K. W. G., *Lancet*, 1957, 2, 663.
[4] Gilliatt, R. W., and Wilson, T. G., ibid., 1953, 2, 595.
[5] Simpson, J. A., *J. Neurol. Neurosurg. Psychiat.*, 1956, 19, 275.
[6] Thomas, P. K., *Neurology (Minneap.)*, 1960, 10, 1045.
[7] Gilliatt, R. W., and Sears, T. A., *J. Neurol. Neurosurg. Psychiat.*, 1958, 21, 109.
[8] Crow, R. S., *Brit. med. J.*, 1960, 1, 1611.
[9] Phalen, G. S., and Kendrick, J. I., *J. Amer. med. Ass.*, 1957, 164, 524.
[10] Heathfield, K. W. G., and Tibbles, J. A. R., *Brit. med. J.*, 1961, 2, 29.
[11] Murray, I. P. C., and Simpson, J. A., *Lancet*, 1958, 1, 1361.

misled by the fact that pain is not confined to the wrist but may spread to the forearm or even to the shoulder.

The syndrome occurs when the capacity of the carpal tunnel is reduced by bony protrusions (osteo- or rheumatoid arthritis, malunited Colles fracture, dislocated carpal semilunar bone, acromegaly), by soft-tissue swelling (chronic or acute tenosynovitis of the flexor tendons, myxoedema), or by oedema (pregnancy, occupational trauma). Perhaps the commonest precipitating factor is obesity in post-menopausal women.[2]

In most cases rapid subsidence of pain occurs when the hand is splinted at night, and this constitutes a diagnostic test. K. W. G. Heathfield[3] and D. Kendall[3] report unfavourably on the pneumatic cuff test.[4] J. A. Simpson[5] introduced an electrical test which is simple and takes little time to carry out. He stimulated the median nerve at wrist and elbow with a brief electric shock and recorded the stimulus and subsequent response of the affected thenar muscles with an electromyograph. He showed that the latency of the muscle response was significantly increased, and that this was entirely due to slowing of conduction in that part of the median nerve passing through the carpal tunnel. The slowed conduction was reversed by operative decompression of the carpal tunnel. P. K. Thomas[6] has applied Simpson's method to 95 cases in which a clinical diagnosis of carpal-tunnel syndrome was suggested and confirms his findings. Both authors found abnormal peripheral slowing of median-nerve conduction in about 70% of cases. Motor fibres may be normal in patients with only sensory loss. R. W. Gilliatt and T. A. Sears[7] extended the method to the recording of action potentials from the nerve trunk after stimulation of the purely sensory digital nerve of the index finger by brief submaximal electric shocks. They found abnormally small nerve action potentials in the median nerve proximal to the carpal tunnel in patients with sensory loss (and sometimes in the absence of objective loss). The latency of the response was slightly increased in more than half of the 23 cases in which it was measurable. These objective tests require special apparatus which should be available in neurological departments. Scrupulous attention to detail is necessary, but the technique is basically simple and there is no doubt that its wider use would add precision to the differential diagnosis of the causes of acroparaesthesia.

Treatment has recently been reviewed by R. S. Crow.[8] Immobilization of the wrist in the neutral position by a close-fitting anterior splint worn at night usually gives immediate relief from symptoms, but relapse is common when splints are discarded. Injection of hydrocortisone into the tunnel is often painful (and the addition of local anaesthetic may make this worse by increasing the volume of fluid injected), but it does give rapid alleviation of symptoms.[9] Chlorothiazide may relieve the syndrome in pregnant patients.[10] These measures are worth trying when temporary relief is acceptable and childbirth or removal from precipitating activities makes spontaneous remission probable. Appropriate treatment of myxoedema cures the syndrome in these cases.[11] Obese patients should have their weight reduced. In all other cases surgical decompression is simple and offers almost certain and permanent relief from sensory symptoms.[8] If there is clinical or electrical evidence of motor-nerve damage, it is advisable to decompress the nerve as soon as possible. Conductivity tests in the post-operative period measure the progress of recovery and give early indication if operation has further endangered the nerve.[5] Physicians will welcome its objectivity.

ACCIDENTAL PNEUMOTHORAX

About 35% of cases of pneumothorax are accidentally caused. This surprisingly high figure comes to light in a recent review by R. O. Antoni and J. L. Ponka[1] of 76 cases of iatrogenic pneumothorax. The subject is of general interest, for cases have been reported after the attentions of general surgeons, otolaryngologists, physicians, and anaesthetists.

The causes may be divided into three groups. The first of these is when air is inadvertently introduced through the chest wall into the pleural cavity. This is usually due to faulty technique in pleural aspiration. The second is when the pleura and underlying lung are punctured. If the pleura alone is damaged the rent usually seals off, but lung puncture will lead to a tension pneumothorax. Damage to the cervical pleura is usually due to a failure to appreciate that the cupola rises nearly 2 in. (5 cm.) above the first rib anteriorly. It may occur when inducing anaesthesia by stellate or brachial block and during surgical operations on the lower part of the neck—for example, during block dissection, tracheostomy, and thyroidectomy. The anatomy of the pleural reflection in the cardiac notch is variable, and pleural or pulmonary damage may accompany paracentesis of the pericardial sac. Mid-line abdominal incisions which pass to the right of the xiphisternum may frequently involve the pleura. Damage may also be produced through the intercostal spaces during such procedures as liver biopsy and radical mastectomy. The same authors point out that the parietal pleura commonly extends below the twelfth rib and may be injured in approaches to the kidney and adrenal or in drainage of a subphrenic abscess. The third cause of accidental pneumothorax is escape of air from a pneumomediastinum. Air in the mediastinum commonly escapes into the pleural cavity or may dissect into the neck, thoracic wall, or retroperitoneal tissues. J. Keis[2] and subsequently H. J. Barrie[3] showed that the air enters the pleural cavity just above the hilum of the lung. The opening is almost certainly valvular and the pneumothorax is of the tension type. Opening of the pretracheal fascia may allow air to enter the mediastinum. G. B. Forbes and colleagues[4] reported a series of tracheostomies in which 25% were followed by pneumomediastinum and 10% by pneumothorax. D. Aiken and

[1] Antoni, R. O., and Ponka, J. L., *Surg. Gynec. Obstet.*, 1961, **113**, 24.
[2] Keis, J. *Münch. med. Wschr.*, 1934, **81**, 669.
[3] Barrie, H. J., *Lancet*, 1940, **1**, 906.
[4] Forbes, G. B., Salmon, G. W., and Herwig, J. C., *J. Pediat.*, 1947, **31**, 1-2.
[5] Aiken, D., and Smith, H. F., *Brit. J. Surg.*, 1953, **40**, 324.
[6] Macklin, M. T., and Macklin, C. C., *Medicine (Baltimore)*, 1944, **23**, 281.

H. F. Smith[5] reported six cases of pneumothorax and two of pneumomediastinum after block dissection of the neck; four of these were fatal. In a series of four deaths due to tension pneumothorax after thyroidectomy Barrie found that the cupola was intact in all cases. Damage to the respiratory mucosa during bronchoscopy or endotracheal intubation may also lead to pneumomediastinum. M. T. and C. C. Macklin[6] point out that excessive pressure in a closed anaesthetic system may cause air to leak into the pulmonary interstitial tissues and thence to the mediastinum.

Diagnosis should present no difficulties if the condition is borne in mind. Many cases presenting with shock and pain in the chest are probably considered to be coronary thrombosis or pulmonary embolism. When the diagnosis has been confirmed prompt therapy is essential. The removal of air from the pleural cavity is most effectively accomplished by thoracotomy and continuous underwater drainage. Needle aspiration may be useful as a temporary measure.

HEPATITIS FROM TATTOOING

Reports in *The Times*[1] that New York tattoo parlours are to close owing to an outbreak of serum hepatitis are a reminder that such establishments have been known to cause the disease before. During the second world war the distinction between infectious hepatitis and homologous serum jaundice became clearly established, though the first intimations of it were noted just before the war. The literature of this period was fully reviewed in these columns in 1949.[2]

Perhaps the first person to attribute serum hepatitis to tattooing was Captain W. T. Hendry, R.A.M.C.,[3] who in 1947 saw 26 cases (and another possible four)[4] believed to have been caused in this way. They were patients in a military hospital in Germany. The report of an Army sanitary inspector who visited the tattooist showed that virus-infected blood could have been transferred from one customer to another. The first reported series of cases seems to have been by Surgeon Lieutenant-Commander R. H. Roberts and Surgeon Lieutenant H. Still, of the Royal Canadian Navy.[5] They described the cases of four patients who had all been tattooed on the same day in the same establishment. In the same year B. F. Smith,[6] of Buffalo, reported seventeen cases of men who had been tattooed at one establishment in Panama City within 49 to 154 days of the onset of symptoms. Two years later Lieutenant-Colonel A. C. S. Hobson, Captain D. E. Fraser, and (the late) Captain N. H. Newman, R.A.M.C., reported[7] from Hong Kong 56 cases of hepatitis among Service personnel who had been tattooed within 51 to 150 days before symptoms started.

Owing to the serious consequences of the disease and the ease with which it can be transmitted a great responsibility rests on tattooists to sterilize their equipment thoroughly. The absence of reports of cases in Great Britain suggests that our own artists maintain proper standards, doubtless with the help if necessary of the medical officer of health. But in New York the city health department has had to take drastic action because, so it is reported, in the past two years thirty cases of serum hepatitis and one death have been traced to tattooing.

[1] *The Times*, October 11, 1961.
[2] *Brit. med. J.*, 1949, **2**, 748.
[3] Robertson, K. M., *Lancet*, 1951, **1**, 57.
[4] Hendry, W. T. Unpublished data.
[5] Roberts, R. H., and Still, H., *Canad. med. Ass. J.*, 1950, **62**, 75.
[6] Smith, B. F., *J. Amer. med. Ass.*, 1950, **144**, 1074.
[7] Hobson, A. C. S., Fraser, D. E., and Newman, N. H., *Brit. med. J.*, 1952, **1**, 1111.

EPIDEMIOLOGY OF THE COMMON COLD

The problems of the common cold are hardy annuals for which no solutions have been found, though recent work has made advances in differentiating the "rhinoviruses" and other agents such as the respiratory syncytial virus.[1] Now O. M. Lidwell and R. E. O. Williams[2] have carried out an epidemiological study of the common cold among office workers in London and Newcastle over a period of six years. They found that about 10% of the colds led to an absence from work with an average duration of absence of 2.6 days. The peak months were October, January, and March. The percentage of colds leading to absence from work increased with increasing age, but the average duration of absence from work was fairly constant in each age group. The sex difference was not large, for females had only 10–15% more colds than males. The use of public transport appears to have been unrelated to the number of colds suffered. Only about one-third of the colds could be assigned to a known exposure to an infected individual in either office or home. In their discussion of this point the authors suggest that some infections produce symptoms too slight to be reported but that these trivial infections are as infectious as the common cold; moreover the infections might be acquired but no symptoms appear until the infection is stimulated by some other event such as weather changes or chilling of the person. Again, if the virus can survive for some days or weeks on textile or other fomites and thence lead to infection, the methods used at present would not show up this source. The many ways in which it is possible to become infected by the virus diminish the possibility of controlling the spread of the common cold. Probably fewer than half of the colds reported were contracted from a fellow office worker, so that attempts to control the transmission of infection there could have only a limited effect.

Data on reinfection after a cold indicated some reduction in susceptibility for a few weeks. There was evidence that antibodies to a particular strain developed in the course of a cold and that susceptibility might be related to the level of antibody activity against that strain. But the possibility of producing a protective vaccine is still not too bright owing to the variety of serological types that exist.

The half-yearly indexes to Volume 1 of the *Journal* and *Supplement* for 1961 are now being dispatched. Members who have not previously asked for the indexes to be sent regularly to them can obtain copies, post free, from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

[1] *Brit. med. J.*, 1961, **1**, 1814.
[2] Lidwell, O. M., and Williams, R. E. O., *J. Hyg. (Lond.)*, **59**, 309, 321.

FUTURE OF THE MENTAL HOSPITAL

A two-day symposium dealing with the future of the mental hospital was held at the Institute of Psychiatry, London University, on October 5 and 6. Sir AUBREY LEWIS welcomed the many psychiatrists who attended it.

In-patient Units

Dr. G. C. TOOTH said that two of the main principles which should underlie the planning of in-patient units for short-stay or indeed any other type of psychiatric patient were, first, that the unit should be readily accessible not only to the population which might need it but also to the local authority services concerned with recognition, prevention, and aftercare; and, secondly, that psychiatry should be linked with general medicine. If those principles were accepted, it followed that a considerable proportion of new psychiatric beds should be planned as part of, or attached to, area general hospitals. At present work was being done on the assumption that 300–400 such beds would be needed per million of the population. But that did not mean that conveniently placed mental hospitals would be prevented from treating short-stay patients. The question of the optimum size for a short-stay unit in a general hospital was difficult. Thirty beds had been suggested as the minimum for the basic unit, but he was inclined to think this too small. There should be enough beds to allow for the classification of patients in terms of behaviour, age, and so on. The size of such units should also be related to the total size of the general hospital. It had been suggested that about 10% of the beds should be psychiatric, and the average area general hospital of the future would have about 800 beds. But in efforts to provide better facilities for short-stay treatment—and Dr. Tooth emphasized that he thought this should have priority—existing hospitals should not be starved of the means of treating and rehabilitating their longer-stay patients.

Dealing with the truly chronic psychiatric patients Dr. Tooth confessed that he was almost entirely without inspiration from the point of view of knowing how they should be provided for in a reformed mental health service. Clearly there would be a number of such people who would need something akin to custodial care in a hospital setting for long periods. Certainly the chronic and especially the brain-damaged psychotic who required no more than custodial care should not be mixed with those who were undergoing active treatment.

The Elderly and the Adolescent

Referring to the elderly, Dr. Tooth said that for many years psychiatrists had been reproached for putting old people into mental hospitals just because there was nowhere else for them to go. It was likely, however, that most of those old people urgently needed psychiatric treatment which could be given only in a mental hospital. The fault, if any, lay with a society that was unprepared or unwilling to take them back after the hospital had done all it could for them. It was expected that many of the old people who formerly came to psychiatric hospitals would in future be treated in the geriatric section of general hospitals under joint geriatric and psychiatric supervision.

Dr. I. HADFIELD (Winchester) asked what provisions would be made for children's hospitals and particularly adolescents' hospitals. Dr. Tooth said that the Ministry would be delighted to bring more in-patient units into being, but the shortage of child-psychiatrists prevented it.

Role of the Local Authority

Dr. J. A. SCOTT discussed the services which the local authority was providing in the psychiatric field. He assured psychiatrists that they would be met more than half way in co-operation from local authorities, and expressed the hope that one of the effects of the Mental Health Act, with its emphasis on community care and voluntary treatment, would be to bring the psychiatric hospital out more into the community. He was not sure, however that either the Ministry or psychiatrists were meeting their proper responsibilities so far as the young psychiatric patient was concerned. He agreed with Dr. Hadfield that it would be a tragedy if two psychiatric services were started. The problem of the geriatric patient was an urgent one, and it was gratifying to see that the Ministry was not only increasing the number of geriatric units but emphasizing the importance of the psychiatric side of the geriatric unit.

Relationship to Other Hospitals

Professor T. MCKEOWN (Birmingham) said that medical services in the past had suffered from being disjointed, and it would be difficult to put matters right unless the various elements in the medical services were seen together as a whole. In the past the medical services had been allowed to change only very slightly in spite of the fact that the problems with which medicine was confronted had changed very rapidly. There were three outstanding issues. The first was the interrelationship between the major classes of hospital, the second the relationship between the hospital and the community, and the third the relationship between curative and preventive medicine. These were fundamental questions, and until some acceptable answer was found to them much of what else was done would be in the nature of patchwork.

Two deep-rooted hospital traditions should be got rid of: the separation of major classifications and the concept of a hospital as a single entity. Professor McKeown suggested that there should be a hospital centre to which all patients would be brought; that they should be catered for in multiple buildings which varied in design, treatment provided, and equipment, and that patients should be classified strictly according to need and without reference to archaic considerations of age, etc. At such a centre the varied services would be available through a common staff. Continuity of care would be ensured by having a single staff with comprehensive responsibilities. Finally, there should be much more intimate relationship between hospital and domiciliary care.

Dr. H. R. VINCENT (Sheffield) thought there were strong clinical advantages in a comprehensive hospital, but the life of the medium-stay patient in a mental hospital was entirely different from the regime of the acute patient. Professor McKeown agreed that there were sharp differences in requirements between the acutely ill and the medium-stay and long-stay patients, but there was a great deal in common between some of the patients who were in mental hospitals and those who were in chronic-sick hospitals. In reply to Dr. B. WARD (Leeds), Professor McKeown said he did not recommend hospitals of 1,500 beds if experience showed that something smaller was desirable. It was, however, possible to have sites with as many beds as 1,500 without the disadvantages traditionally assigned to them.

Need for Rehabilitation

Dr. J. K. WING, of the Medical Research Council's Social Psychiatry Research Unit, said that they had been investigating the problems of rehabilitating mental patients, particularly chronic mental patients; these mainly included schizophrenics, who comprised three-quarters of all long-stay patients. In one survey of three London mental hospitals, in 1951 there were 450 schizophrenics admitted, on average spending (including readmissions) 17 months in the hospitals. In 1956, 715 patients were admitted, spending 11 months in the hospitals. These were both in the three-year period following first admission. However, as the number of first admissions had not gone up, the figures showed that although the length of stay was going down the chance of readmission was going up. Dr. Wing said that they had been disturbed to find that on each occasion of readmission the patient spent significantly longer in hospital than on the previous occasion. As a result of

another survey there was evidence that during the follow-up period there were signs of morbidity, disturbed social behaviour, and violence. One was left with the feeling that schizophrenia was still a very chronic disease.

Rehabilitation was concerned primarily with chronic disabilities, and as a result the patient was going to be in touch with rehabilitation services for years; therefore the number of patients was going to accumulate, if not in hospitals then in the community. As an example of what could be done in the way of rehabilitation, he gave Bristol, where there was not only work in the mental hospital but also a rehabilitation workshop outside the hospital. The plan was that the patient could go on to live in a council house built by the local authority, and he could work in one of the local firms.

Hospital Design

Professor R. Llewelyn Davies spoke on the design of the psychiatric hospital from the architect's point of view. Most mental hospitals in this country, he said, had been built before the first world war, and were well designed "for the custodial care of the maximum number of patients by the minimum number of staff." The two main publications on modern trends—a W.H.O. report and one from the United States by the Group for the Advancement of Psychiatry—both focused on the question of size and numbers, and both referred to numbers of the order of 300 or 500 as being the maximum size. The interior should be planned to accommodate groups of six to twelve. Where possible there should be small units of living accommodation, divided from the next unit by open ground or a communal area. There had been a slight shifting of view recently, Professor Davies continued, suggesting the bringing of mental care into the ambience of the general hospital, in which case the problem would be modified, as certain facilities could then be used by both the general hospital and the psychiatric hospital; wards could be used by certain groups of mental patients, or for a certain period of their stay.

Care of the Subnormal

Dr. J. Tizard said that in recent years the proportion of seriously handicapped patients, the idiots and imbeciles, had increased, whereas the proportion of subnormal or feeble-minded patients had diminished; this was due to better educational services, better social services, and full employment. So far as planning was concerned, this was handicapped by the absence of adequate statistics. The Ministry collected only a minimum of information for routine statistics. There was very little in the way of national figures. The question of how many beds should be provided for the mentally defective depended upon the prevalence, and upon the quality and quantity of other services, and also on the attitude of the doctors and the public. Two types of patient were now generally recognized, the long- and short-stay patients. What had been called the middle-stay patient had not received much attention; very little had been done to find out how many patients could be rehabilitated after one, two, or five years' time.

He thought it very unlikely that comprehensive hospitals would meet the needs of the mentally defective. What he would like to see tried out would be to take the patients by degree of handicap and give them different services according to that degree. The most seriously handicapped people were the idiots, particularly idiot children; he would like to see them in units associated with paediatric hospitals. One solution of the problem—he thought it a practical thing which could be experimented with—was that such patients should be in small annexes attached to paediatric departments, and they should stay there until such time as the paediatrician felt he could no longer deal with them. So far as imbecile children were concerned, Dr. Tizard thought the majority of their problems were very similar to those of much younger normal children. In an experiment with imbecile children between 4 and 10 years of age and normal children it was found that the imbecile children did develop. With regard to cost, it had been found in Denmark that the bigger the place the more it cost per head. So it appeared that small centres were just as economical as large ones.

In the discussion Dr. W. Wollen (Dartford) said that there were now more "low grades" nearly from birth, and they had to be cared for practically all their lives. The problem was how to fit this large group of people into the community.

Day Hospitals

The last speaker was Mr. W. A. J. Farndale, deputy house governor at Maudsley Hospital, who pointed out that the day hospital was a post-war development, the first one operating in 1946. This was part of the trend towards treating patients at the hospital rather than in it. There were three types of day hospitals: psychiatric; geriatric, for physical infirmity; and the day centre for physical rehabilitation. It was claimed that certain patients could be treated as successfully by the day as when in-patients, and certainly rehabilitation was made easier. Some patients could be transferred to day hospitals as they progressed. The initial cost for a day hospital was less, because less space was required, the staff worked only five days a week, and only two meals a day were provided. The scheme was popular with the nursing staff. However, there was need for careful selection of patients.

A relatively large number of day hospitals, continued Mr. Farndale, were attached to general hospitals; they had often begun in the out-patient department carrying out occupational therapy, and then the need had arisen for a separate section. It was probable that this trend would continue, especially as the day hospital could treat in-patients and both internal and external day patients. Day hospitals might in the future play their part in furthering the reduction of the number of psychiatric beds required.

Asked about the capital outlay for a day hospital, Mr. Farndale said it worked out at about £600 a place. A building for 50 places should not cost more than £30,000. Running costs varied between £10,000 and £20,000 a year, including the salaries of consultant staff. Dr. R. H. Wheeler asked if there was any Act under which a day centre could be opened for elderly people. The speaker replied that legislation was now before Parliament to enable local authorities to develop day centres for elderly people.

Dr. D. L. Davies, dean of the Institute, in summing up the issues raised by the symposium, said there appeared to be a very definite problem of how the mental hospital should fit into the overall services for the mentally ill in the future. He had been thrilled by Professor McKeown's rethinking of the whole problem from first principles.

Because of the advances made in recent years in electronic hearing-aids and in the methods of training very young children whose hearing is impaired the Minister of Health, Mr. Enoch Powell, believes that some revision of the local authorities' welfare services for the deaf and hard-of-hearing is needed. County councils and county borough councils have accordingly been informed that the Advisory Committee on the Health and Welfare of Handicapped Persons recommends that all persons who suffer from a disabling loss of hearing should be regarded as forming a single class which for registration for welfare services should be subdivided into the deaf without speech, the deaf with speech, and the hard-of-hearing. From January 1 their registers should be revised on these lines. It is suggested that authorities should devote particular attention to the needs of the increasing group of the deaf with speech which for some time will consist largely of younger people who need facilities for continued auditory training and speech practice and whose other welfare needs are similar to those of the hard-of-hearing.

ARTHROPOD-BORNE VIRUSES

SYMPOSIUM IN BRAZIL

[FROM A SPECIAL CORRESPONDENT]

Those who decry the climate of the British Isles may take comfort in the thought that there are disadvantages in living in warmer regions, particularly when infections carried by mosquitoes and other blood-sucking arthropods are considered. The arthropod-borne or "arbor" viruses now number about 150 different agents, of which only one, louping-ill virus, occurs within the British Isles. No fewer than 40 of the 150 different arthropod-borne viruses have been found in Brazil, most of them within the past six or seven years as a result of the activities of the Belem Virus Laboratory, which is operated jointly by the Rockefeller Foundation and the Serviço Especial de Saúde Pública of Brazil. It was therefore appropriate that the Brazilian Medical Association should have chosen the theme of the arbor viruses as the subject for a symposium which was held in Rio de Janeiro last month in association with the 15th meeting of the World Medical Assembly.

Distribution of Arbor Viruses

Dr. CALIXTO E. CAUSEY, of the Belem Virus Laboratory, reviewed the viruses known to be present in Brazil against a background of their distribution throughout the world. The 150 or so different arthropod-borne viruses were placed, he said, in 15 serological groups, viruses within a group being somewhat interrelated, but there was no serological relationship between viruses in different groups. The first three groups had been allocated letters, A, B, and C, but the remaining groups were called after the first or most important member of the group to be recognized. Of about 20 viruses in Group A, six—Eastern, Western, and Venezuelan Equine Encephalitis (E.E.E., W.E.E., and V.E.E.), Aura, Mayaro, and Una viruses—had been found in Brazil. Group B contained about 25 agents, of which yellow fever, Bussuquara, Ilheus, and St. Louis viruses had been found in Brazil. The recognition of Group C viruses was almost entirely due to the activities of the Belem Virus Laboratory, which had established the presence of six different Group C viruses. Further Group C agents not known in Brazil had recently been isolated in Trinidad, and antibodies against Group C viruses had been detected in human sera collected in West Africa. Three viruses in the Bunyamwera group—Cache Valley, Guaroa, and Kairi—and two in the Guama group—the prototype Guama and another strain, Catu—had also been recognized. The other viruses fell into smaller or less-well-studied groups and include Oropouche (Simbu group), a virus of the Turlock group, first isolated in the U.S.A. and since found also in India, viruses of the Tacaiuma group, and at least five other unidentified agents.

Human Bait and Sentinel Mice

Further details of the work of the Belem Virus Laboratory were provided by Dr. O. R. CAUSEY. From the opening of the laboratory in November, 1954, until December, 1960, 1,600 virus strains had been isolated. In certain instances the same agent was recovered from a number of different specimens so that the total number of separate isolations was less. About 5% of all viruses studied proved not to be arthropod-borne upon further examination. Material was obtained from man and domestic animals with febrile illnesses, from trapped wild animals and birds, from arthropods caught using live animal or human bait, and by the use of sentinel animals. Yellow fever, Mayaro, and Oropouche viruses were isolated from epidemics affecting man, and other viruses have been recovered from single human cases in the forest zone. E.E.E., Bussuquara, and Guama viruses have been responsible for epizootics, the first in horses and the second in fledgling wrens. No virus had been recovered from 200 specimens from reptiles or amphibians, but 57 agents were isolated from arthropods, an average of about one infected mosquito in 4,800, rising to 1 in 800 during epidemic or epizootic periods.

The use of sentinel mice had been a particularly fruitful approach. A cage containing six newborn mice and the mother was suspended in the forest so that it was protected from rain and large animals but so as to allow free access to mosquitoes. Infant mice were highly susceptible to many arbor viruses by peripheral inoculation or by mosquito-bite. More than 700 isolations had been obtained by this method. The problems of handling and identifying the large number of viruses isolated in Belem were discussed in a paper by Dr. R. E. SHOPE, presented in his absence by Dr. O. R. CAUSEY.

Yellow Fever and Urban Epidemics

Drs. H. LAEMMERT and O. R. CAUSEY reported on yellow fever in the Amazon region. Twenty isolations of yellow-fever virus had been obtained from human cases and four from mosquito-suspensions during the period 1954–5, but since that time the only isolation of the virus was from a sentinel monkey placed in the forest.

The way in which a virus which was circulating in forest animals might produce a sharp epidemic if it was introduced into an urban area was illustrated by a paper presented by Drs. F. and M. PINHEIRO, G. BENSABATH, O. R. CAUSEY, and R. E. SHOPE. Two strains of Oropouche virus were isolated during May, 1960, the first from forest mosquitoes (*Aëdes serratus*) and the second from the blood of a sloth. Later, 16 strains of the same virus were isolated from 15 patients all living within the township of Belem (one patient yielded two strains on different days). The clinical picture was of fever, sometimes severe, with pains in the back and photophobia in three cases. The duration of the illness varied from two to seven days, and no patient was sufficiently ill to be admitted to hospital. All those from whom virus was isolated, and 40 of 72 others bled after the outbreak showed antibodies against Oropouche virus in mouse-protection tests. The high attack rate suggested that the virus had not previously affected town dwellers, although activity in the forest appeared to be widespread. A virus isolated from a liver biopsy taken from one of the non-fatal cases was later identified as a strain of Guaroa virus.

Drs. O. DE SOUZA LOPES and J. P. G. DE LACERDA reported the isolation of a virus from sentinel mice placed in the forest at Cotia, near São Paulo. Forty separate isolations were all considered to be strains of the same agent. Preliminary tests had failed to establish any relationship to viruses of Groups A, B, C, Bunyamwera, or Tacaiuma. Further studies on the agent were under way.

Tissue-culture Techniques

Different aspects of research on arthropod-borne viruses were dealt with by speakers from outside Brazil. Dr. J. S. PORTERFIELD, of the National Institute for Medical Research, London, showed how tissue-culture methods could be applied to the detection of antibodies against arthropod-borne viruses. Three modifications of plaque methods using chick embryo cells were described. The methods worked well with more than 15 different Group A viruses and had been used to examine human sera for the presence of antibodies to O'nyong-nyong virus following an epidemic of that disease in Uganda. Group B viruses were technically more exacting, but satisfactory results had been obtained with yellow fever, West Nile, Ilheus, and Israel turkey virus, as well as with members of the tick-borne complex. Tissue-culture methods provided a valuable additional tool for the identification of new viruses and offered practical advantages over mouse-neutralization tests in the examination of large numbers of sera for survey purposes.

Five Clinical Syndromes

Dr. G. O. Broun, of the Department of Medicine, St. Louis University, U.S.A., divided the diseases produced by arthropod-borne viruses into five clinical syndromes. The first included those which produced only a mild systemic infection. The second syndrome presented hepatitis as the outstanding clinical feature, the most important virus in this category being yellow fever. The third clinical grouping included those conditions in which myalgia, arthralgia, and a skin rash were notable; dengue and West Nile fevers came into this category. The fourth class included a group of haemorrhagic diseases, Omsk, Crimean, and Far Eastern haemorrhagic fevers, and some, but by no means all, cases of Kyasanur Forest disease in India. Finally there was the group in which the infection affected the central nervous system, including the important mosquito-borne and tick-borne encephalitides. A difficulty about a clinical classification of the arbor virus infection was that the same virus might produce a mild systemic illness in one individual and yet give rise to a severe encephalitis in another, so that a diagnosis on purely clinical grounds was extremely difficult except in times of an epidemic with a particular virus.

Tick-borne Encephalitis in Europe

The laboratory diagnosis of tick-borne encephalitis in Central Europe was discussed by Drs. H. G. Schatzmayer, C. Kunz, and H. Moritsch on the basis of studies carried out at the Hygiene Institute of the University of Vienna. Using a variety of serological tests it had been possible to demonstrate antibodies against tick-borne virus in about one-half of all patients with disease of the central nervous system in the area in south-eastern Austria under study. Dr. Moritsch said that in the younger patients the illness followed a meningitic type of infection, whereas the older subjects more commonly showed paralyses. Most of the cases occurred in the spring and virus had been isolated from ticks in the endemic area, yet only about one-third of all cases admitted having been bitten by ticks.

The final session of the symposium was a plenary meeting with delegates attending the World Medical Assembly. Speakers stressed the world-wide distribution of the arthropod-borne viruses together with the need for an approach on several different fronts, ranging from clinical medicine, public health and epidemiology, entomology, and mammalology, quite apart from the many different aspects of virology. This whole field is expanding very rapidly, and the meetings served a useful purpose in making these advances more generally known.

"I was astonished to discover in our survey that a body which employs something like 500 part-time doctors and 600 part-time nurses and serves 200,000 women a year in over 300 clinics should employ no more than 200 other workers in all its clinic services—and nearly all of these are employed less than half-time and paid little more than nominal sums. We found only seven full-time, fully responsible branch or clinic administrators in the whole service and only about 42 similar part-time administrators. Most of these and other employees, we found, are concentrated in 19 branches which between them operate 56 clinics. It is a remarkable and wonderful fact that the clinics are kept going by some 2,500 unpaid women workers who do all the non-medical chores and are supported by 2,300 other men and women—mostly women—who participate in the committees. What of the future? The scale and complexity of clinic work is growing, there is going to be a wider variety of medical procedures in the clinics, new methods of work will be required if husbands and male doctors are brought in—all this points to a rather more sophisticated management, at least in the larger urban centres, and to the need for a larger establishment of paid office staff and administrators." (Professor F. Lafitte, "Taking a Look at the F.P.A.," *Family Planning*, October, 1961.)

MEDICAL SCHOOL OPENINGS

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE

Mr. H. J. Seddon, director of studies, Institute of Orthopaedics, chose the theme "Time and Leisure" for his inaugural address to the Royal Free Hospital School of Medicine on October 4. He selected a library of masterpieces and literary gems—thanks to paper-backs—as leisure-time reading for students, and added two other important activities: physical exercise and religious worship, the latter often having to compete with the cheap press and films. On the academic side, Mr. Seddon said that wherever there was a choice between reading or going to see something relevant to a particular issue it was better to go and observe. A patient would not come into the consulting-room carrying a sheet of pathological reports; every one of our senses—except that of taste—should be constantly in use throughout the student's observations. He disliked hearing the terms "killing time" and "marking time." Both phrases indicated a throwing away of the most priceless commodity. But however busy the student might be he should still find time for leisure in order to be a balanced person. Sport of some kind was particularly important for young people living in a city.

In her annual report Dr. Katharine Lloyd-Williams, dean of the School, congratulated Miss Roma Ashby on representing British universities at the World Student Games held at Sofia, and on retaining the Women's A.A.A. Championship title for the mile. It was announced that at the end of the 1961–2 academic year Dr. Lloyd-Williams would be resigning from her office and that Dr. Frances Gardner would succeed her as dean.

INTERNATIONAL FEDERATION OF SURGICAL COLLEGES

The International Federation of Surgical Colleges held its fourth Annual Meeting in Oslo from September 12 to 14 under the auspices of the Norwegian Surgical Association.

Meetings were held in the house of the Norwegian Medical Association and in the University of Oslo. Twenty different member-colleges were represented and new members admitted were the Argentine Surgical Association, the Association of Surgeons of East Africa, the Israel Surgical Society, and the Spanish Association of Surgeons. Sir Harry Platt was re-elected President and Mr. Kennedy Cassels was re-elected Secretary and Treasurer for the ensuing three years. Professor Carl Semb (Norway) and Professor J.-L. Lortat-Jacob (France) were re-elected members of the Executive Committee. It was decided to stimulate member-colleges to set up in their own countries committees designed to collaborate with the national Red Cross Society in recruiting emergency surgical teams when necessary. Arrangements were also confirmed for periodical meetings between the International Federation and the World Health Organization and the League of Red Cross Societies for discussion of matters of common concern.

Working Party Reports

The Council received reports from its four Working Parties on the Training of Surgeons, on Surgical Research, on Surgical Missions, and on Interchange of Young Surgeons. The following resolutions, among others, were passed: (1) that in the education and training of the young surgeon due attention should be paid to the importance of experience in the organization, scope, and techniques of the auxiliary services; (2) that research on surgery and chemotherapy as a combined therapy against malignant diseases should be further encouraged by members of the

(*Continued at foot of page* 1082)

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Lubricating Jelly and Granulomas

Surgical lubricating jellies are generally regarded as bland innocuous substances which produce no tissue reaction. Consisting basically of sodium alginate or tragacanth in combination with glycerin and a mild antiseptic, their widespread use without untoward local effect supports this view. Nevertheless it now appears that their entry into the tissues through a breach of the mucosal surface to which they are applied may occasionally lead to granulomatous lesions. R. J. Reed and his associates[1] have reported five cases from New Orleans in which peri-urethral granulomata developed after the use of standard lubricating material for urethral instrumentation. Four of these were cases of stricture while the fifth presented difficulty on account of an enlarged prostate; it is reasonable to assume that trauma played an important part in all. Histologically the lesions were characterized by areas of basophilic amorphous material surrounded by macrophages and foreign-body giant cells. The staining reaction of the amorphous material resembled that of the lubricating jelly which had been employed. Similar lesions were observed in rats after the subcutaneous injection of samples of two standard lubricating jellies.

While experimental work suggests that much permanent scarring is unlikely, the temporary reaction may occasionally lead to serious consequences. Furthermore as the result of trauma lubricating material may be forced into the local blood-vessels and be transmitted in the circulation to the lungs. In two of the cases described masses of basophilic material like that detected in the peri-urethral tissues were discovered in the terminal pulmonary vessels and were regarded as a contributory cause of death in one. Additional evidence of the occasional entry of intraurethral instillations into the local circulation was afforded by a final case of stricture, where, following forcible urethrography, the contrast material appeared in the pelvic veins.

Though there can be no doubt from the widespread use of lubricating jellies without ill-effect that such complications are infrequent, these observations sound a note of caution against their careless administration. Undue force should be avoided both in injection and during any subsequent instrumental procedure.

REFERENCE

[1] Reed, R. J., Smith, J. L., and Steinberg, W. H., *Amer. J. clin. Path.*, 1961, **36**, 41.

(*Continued from page* 1081)

Federation; (3) that the attention of the World Health Organization be drawn to the importance of the universal problem of infection in hospitals and that W.H.O. be asked to support research programmes pertaining to the aetiology and prevention of hospital infections; (4) that research on mass casualties from irradiation should be handled on a national rather than an international basis, and that research on long-term storage of whole-blood or plasma, or the development of better plasma substitutes, should be encouraged; (5) that the International Federation should encourage the interchange of young surgeons between the countries represented in the Federation.

A discussion was held on "How Can the International Federation Foster Surgical Research on an International Basis?" the principal speakers being Professor I. S. RAVDIN (U.S.A.) and Professor DIGBY CHAMBERLAIN. Communications on recent research work were read. A dinner was held at the Continental Hotel at which the company (97 in number) were welcomed by Dr. GUDMUND SEMB, local secretary of the meeting, and the speakers were Professor CHRISTIAN BRÜÜSGAARD, President of the Norwegian Surgical Society, and Sir HARRY PLATT.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Finger-tip Injuries

SIR,—I have just read Mr. F. J. Moynihan's admirable article "Long-term Results of Split-skin Grafting in Finger-tip Injuries" (September 23, p. 802) and also my colleague Mr. Charles McCash's thoughtful comments on it (October 14, p. 1021).

As Mr. Moynihan points out, partial or complete amputations of the finger-tip are probably the most common of the important injuries of the hand. Any estimate of the total annual incidence is a guess, and a wild one; but if the Guy's figures are representative then this guess can be made as follows: traumatic amputations of the finger-tips constitute about 1% of some 20,000 new casualty attendances a year at Guy's. If the annual incidence in the nation of new casualty attendances (both accident and acute sick) is about 10 million then the figure for traumatic amputations of the finger-tips is about 100,000 annually. However accurate or not this figure may be, the commonness of the injury is certain, as is the poor level of general results of primary treatment up and down the country.

Mr. Moynihan makes all the necessary points in his critical assessment of the technical value of split-skin grafts as a primary method of repair used at Guy's for the last 15 years. His results of primary repairs done for patients, many of whom have done heavy manual labour for five years, confirm the value of this simple method of wound-closure, and provide evidence of the inaccuracy with which the method has so often and so intemperately been condemned—generally by special clinics. As in the treatment of so many types of injury, there is a clear distinction between what is ideal and what is practical. Mr. Moynihan agrees with the superior quality of cross-finger and thenar-flap repairs, but rightly insists upon obvious safeguards—safeguards which cannot always be present and which limit their use in the great majority of patients with these common injuries. He also says that primary split-skin grafts can often be a definitive repair of excellent quality in function and appearance.

Training of dressers in "tissue craft," particularly in the basic plastic methods of soft-tissue repair, with adequate supervision and after reasonable instruction, is often deficient. The open accidents treated definitively in casualty departments of teaching hospitals can supply experience in "tissue craft" for dressers not otherwise available. Mr. Moynihan's article shows that this genuine teaching advantage can be obtained not only without risk to the patient but to his clinical advantage.—I am, etc.,

London W.1. PATRICK CLARKSON.

SIR,—I feel that Mr. F. J. Moynihan's paper (September 23, p. 802) calls for some comment. I think Mr. Moynihan has shown that the split-skin graft has a place in the treatment of finger-tip injuries under conditions in which his cases were treated. It is not open to doubt that these grafts take readily and therefore the time off work may be reduced to a minimum by their use. In this context I must point out that Mr. Moynihan has misquoted me when he states: "Reid

(1956) found[1] found the average disability after split-skin grafting to be between seven and eight weeks." The disability period referred to in my paper concerned *full-thickness* grafts—i.e., Wolfe grafts. It is recognized that these grafts require longer to consolidate than split-skin grafts and this fact accounts for the longer disability period resulting from their use. The long-term results, however, are superior to those achieved by split-skin grafts.

Mr. Moynihan puts forward split-skin grafting as a satisfactory method of treatment in the casualty department for all finger-tip amputations. It would appear to me that expediency plays a prominent part in advocating such a policy. For example, he mentions the large number of open hand injuries attending the casualty department, the inexperience of casualty officers, the training of students, and so on. Surely in these days. when we are aiming at the more efficient treatment of hand injuries, minor as well as major, a policy of expediency is to be deplored. In one paragraph Mr. Moynihan states that finger-tip amputations are a major source of casualty attendance, yet in a subsequent paragraph the number of these injuries treated is stated to average two a week. A hand-surgery service, which must inevitably be closely linked with the casualty department, should be able to take this in its stride and treat each case purely on its merits.

I maintain in hand surgery that it is wrong to treat a type of injury, in this case finger-tip avulsion, by the same method in every case.[2,3] Each case should be carefully assessed. The level of amputation, the occupation of the patient, the texture of the hand-skin, and his age are all factors which should guide one as to the type of repair indicated. Loss of skin or minimal pulp may satisfactorily be repaired by free graft, be it split-skin, full-thickness skin, or toe-pulp. A more extensive loss involving bone in a skilled craftsman is best treated by a thenar or cross-finger flap. In such a case precision work demands supple fingers with pulp and skin of good sensory quality. In my experience this may only be achieved by a flap as described. A similar case in a labourer with horny skin might well be best treated by shortening the finger.

I entirely agree with Mr. Moynihan that finger flaps require "most careful attention to detail, good facilities, and time," all of which should be available in a hand-surgery service. Performance of these procedures by inexperienced persons under poor conditions cannot be too strongly condemned. Such can only bring disrepute to these excellent procedures. Incidentally, some years ago I recorded a disability period of under five weeks in fifteen consecutive thenar repairs.

Finally, a word in support of the casualty officer. Many casualty departments are now staffed by senior casualty officers—men of considerable surgical experience. They should form a valuable link in the hand-surgery service. This liaison between the casualty department and the hand-surgery team is absolutely essential if the so-called minor hand cases are to receive the treatment they deserve. Hand surgery demands a flexible approach and a full knowledge of all the available techniques which may be applied.—I am, etc.,

Plastic and Jaw Unit,
United Sheffield Hospitals. D. A. Campbell Reid.

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Intramuscular Injections

Sir,—Your annotation (September 16, p. 758) does not include an important objection to the vastus lateralis —namely, that here an injection is usually painful. This is more noticeable in men than women. Not only is pain experienced as the needle pierces the fascia lata, but also the inflow of even 1 ml. of a bland liquid may cause pain. I suspect that this is due to the lack of distensibility because of the thickness of the overlying fascia.

I have followed for many years Grey Turner in advising this site, but I now believe this to be wrong. Mr. F. G. St. Clair Strange (October 7, p. 956) has convincingly explained why mishaps arise from gluteal injections, especially when given by nurses. With correct teaching and injection into von Hockstetter's site of election (anterior gluteal) both comfort and safety can be achieved.—I am, etc.,

London W.1. A. H. Douthwaite.

Sir,—I would be obliged if you would allow me space to support the late Professor Lambert Rogers's plea (October 7, p. 956) for the adoption of the outer side of the thigh as the site of election for intramuscular injection. It is several years since the traditional site in the buttock was abandoned in the casualty department and elsewhere in the Royal Gwent Hospital, Newport. In my department, at least 20,000 intramuscular injections are given every year, and since adopting the outer side of the thigh as the site for injection there have been no complications either in the form of haematoma formation or otherwise. In contrast to this, in addition to the neurological complications mentioned in previous letters, one can recall many cases in which broken needles had to be retrieved from situations demanding difficult anatomical dissections involving long and tedious operations. These would have been avoided had the offending needle been inserted into the thigh rather than the buttock.—I am, etc.,

Casualty Department,
Royal Gwent Hospital,
Newport. R. Vernon Jones.

Sir,—May I strongly support the plea by the late Professor Lambert Rogers (October 7, p. 956) that the safest and best place for intramuscular injections is the outer side of the thigh? Many years ago I treated a large number of cases of schizophrenia by means of repeated intramuscular injections of sulphur suspended in olive oil. The viscosity of the solution was such that very large-bore needles were necessary, and, because the injections were to be given subperiosteally, the site chosen was the middle of the outer aspect of the thigh and the needle inserted until its point struck the femur.

Although of course the rationale of that treatment was to produce a subperiosteal irritation with inflammation and pyrexia, I do not ever recall the procedure producing a haematoma in the vastus externus, and most certainly no harm produced by the needle striking the femur.—I am, etc.,

Pyle, Glam. R. J. Phillips.

Sir,—I would like to draw attention to a further "refinement" in intramuscular technique, which is apparently little known and which is not mentioned in your annotation (September 16, p. 758). The

conventional, deliberate, and comparatively slow introduction of the needle with syringe attached is replaced by an instantaneous introduction, which is always completely painless. The needle is held by the butt between the thumb and second and third fingers exactly like a dart, and is plunged into the tissues as fast as possible with a downward flick of the wrist. The syringe is then attached for the injection. I was first introduced to this method by a staff nurse who demonstrated it on my person. *O! si sic omnes.*—I am, etc.,

East Glamorgan Hospital, Near Pontypridd. J. DE SWIET.

Neuropathy after Thalidomide ("Distaval")

SIR,—I read with interest the article by Drs. Pamela M. Fullerton and Michael Kremer (September 30, p. 855). I have seen six cases of neuropathy due to "distaval" (thalidomide) this year; in fact it seems that this drug is fast becoming one of the commonest causes of peripheral neuropathy in neurological clinics. When this neuropathy occurs with other neurological disease diagnosis can be difficult. One of my patients has cervical spondylosis, another diabetes mellitus, and yet another post-encephalitic Parkinsonism; in these three, however, the neuropathy is purely sensory and there is slight sensory impairment in the distal parts of all four extremities without other physical signs, the reflexes being normal. One has learnt to recognize this clinical pattern as typical of distaval neuropathy.

It is of some interest that the makers of this drug, while admitting that neuropathy occurs in 1 in 250 cases of patients on long-term therapy, still advertise it widely as the ideal hypnotic and it even occupies a prominent page in the current number of the *Journal of Neurology, Neurosurgery, and Psychiatry*.

Like Drs. Fullerton and Kremer's cases, mine have so far not improved greatly when the drug has been withdrawn.

It is clearly important that wide publicity is given to this neuropathy, for the drug is still very popular. One source of confusion has been the use of the official name, for the first description of distaval neuropathy appeared in the *Journal* under the somewhat unhelpful title of "Is Thalidomide to Blame?"[1]—I am, etc.,

Whipps Cross Hospital, London E.11 K. W. G. HEATHFIELD.

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SIR,—I was most interested to read the article by Drs. Pamela M. Fullerton and Michael Kremer on neuropathy after the intake of "distaval" (thalidomide) over a long period (September 30, p. 855).

I have for the past 18 months been perplexed by a female patient of 35 who has complained of paraesthesiae in the hands and later in the feet spreading upwards over the months to the groin. There was also gradually increasing pain in the limbs and weakness of the legs with difficulty in climbing stairs and walking. Oedema of the ankles has been present on occasions. An interesting factor present in this case and not noted in the article, probably owing to the age group of the reported cases, was that amenorrhoea occurred after starting to take thalidomide in doses of 50–100 mg. nightly. From regular daily temperature charts it was apparently associated with the absence of ovulation. Two dilatations and curettages at intervals of 12 months showed normal pelvic organs but little or no curettings. Brittle finger-nails with marked ridging were also noticed.

It would be interesting to know whether the amenorrhoea is also due to taking thalidomide over a long period, as all the other symptoms presented in the article are practically identical with those in my case. It should perhaps be added that the presence of any other neurological condition has been excluded.—I am, etc.,

Nuneaton, Warwickshire. PHILIP HOWE.

Seasonal Incidence of Clinical Onset of Hodgkin's Disease

SIR,—Dr. Marion D. Cridland (September 2, p. 621) has reported that the times at which patients present with symptoms of superficial Hodgkin's disease are not randomly distributed among the months of the year; and her finding has since been confirmed by Drs. James Innes and Joseph Newall (September 16, p. 765) in a further series of cases. Dr. Cridland has suggested what the later authors hesitate to accept, that this consistent seasonal preponderance of cases presenting might support the view that Hodgkin's disease is caused by an infective agent or that its onset is precipitated by such an agent.

Drs. Innes and Newall have intimated that the time between initiation of a tumour and its attainment of a clinically significant size is an expression of its growth rate. If it is assumed that the disease is initiated at a single minute focus and that a single affected gland is to triple its normal volume by proliferation of the cells in the initial focus, then a growth rate overwhelmingly greater than the usual rate of progress of the disease indicates must be construed if initiation of the disease and presentation of a slightly enlarged gland are to occur within a few weeks of one another. Furthermore, it is evident that sites remote from the primary must already be involved at the time the patient presents; otherwise the disease could be cured by excision of the primary focus. Nevertheless, these secondary sites often do not achieve a detectable size until many months after the first symptom.

Dr. Cridland's paper raises yet again the question of the status of the "infective" theory of the origin of Hodgkin's disease, and since the status of this theory of aetiology seems to enjoy indefinite immunity to the growing evidence of failure to isolate a specific causative agent the matter deserves further discussion at the present time.

Hodgkin's disease can make its first appearance in a wide variety of sites, many of which are unrelated to a recognized portal of infection; sooner or later it is found to have spread widely through the body by a process indistinguishable from multiple metastasis; the lesions are characterized by cellular proliferation, by abundant production of aberrant tissue (neoplasia), and by infiltration of normal structures; progress of the disease is checked by forms of therapy (e.g., radiation and nitrogen mustard) which are known to restrain the course of malignant disease and to act by interference with cellular proliferation; the disease may shade off into a condition from which the histologist cannot withhold a frankly malignant appellation—Hodgkin's sarcoma; and, finally, it is invariably fatal. Where is the decisive distinction from an early-metastasizing form of malignant disease?

The "infective" theory of origin appears to rest on very slender associations: classical confusion of the disease with tuberculosis; the existence of cellular pleomorphism in the

lesions; and the occurrence of systemic manifestations such as fever, anaemia, or a rash. But it would indeed be surprising if spontaneous manifestations of the reaction to infection, or abnormal reactions to actual infection, were not to be observed during the course of a disease, of whatever origin, that disorders the very tissue that is most intimately involved in the response to infection. It should be added that there must be very few human diseases which have been so intensively explored for the implication of a microbe in their aetiology. The enormous literature on the subject reports little more than a series of trials of innumerable suspects ranging over almost all the species of parasitic unicellular organisms.[1] The evidence has never been sufficient for a conviction, although many of the suspects were on trial for several years before being reluctantly discharged as innocent. It is not unreasonable to conclude that the instigation for most of these many inquiries may not have been sound.

It follows that there is a greater volume of negative evidence against the "infective" origin of Hodgkin's disease than against an infective cause for cancer of the rectum or for chilblains. With every regard for wise counsel to keep an open mind in the matter, it can reasonably be asserted that since the grounds for belief in the "infective" theory have grown no larger, whereas the negative evidence against it has been cumulative for over half a century, the time has come when the "infective" and "neoplastic" theories should not be given equal status in textbooks of pathology. Is there *no* weight in negative evidence? The matter is of more than academic interest: obsession with the "infective" theory has absorbed, and is still absorbing, an excessive proportion of research zeal in the subject, with relative neglect of other aspects of the disease.

The undying attractiveness of the "infective" theory may owe much to two factors which spring more from the forgivable foibles of human nature than from the observable features of the disease: first, the theory promises to bring this lethal condition into the category of diseases over which we are steadily achieving specific mastery; secondly, it offers a methodologically and intellectually more comfortable experimental approach than does the consideration of an intrinsic origin. That is, the subject is less encouraging and more difficult without a microbe in the picture.

With regard to Dr. Cridland's findings, it is relevant to observe that suicide, a wilful act, consistently shows an incidence which also is not randomly distributed among the months of the year.[2,3] The decision to seek advice about a symptom of rather gradual onset is also a wilful act. As your correspondent, Dr. K. W. Beetham (September 30, p. 896), points out in a light vein, seasonal circumstantial factors are a recognized influence on personal decisions of this kind.

Finally, may I be permitted to recommend retirement of the term "lymphadenoma"? "Adenoma" is well established as a term for benign tumours of glands; the lymph node is not a gland; the lesions of Hodgkin's disease have no glandular structure; and the disease is most certainly a malignant disease.—I am, etc.,

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Cytotoxic Drugs and Radiotherapy

SIR,—I attended the symposium on the subject of methotrexate in the treatment of cancer described in your special correspondent's report (October 7, p. 954). The primary disappearance of disease by continued intra-arterial infusion with methotrexate direct to the tumour has been shown to be truly remarkable in many cases as yet of limited duration. In 1959 I made an unchallenged statement in your columns to the effect that "cytostatic" remedies have never really cured a malignancy."[1] In the main this is still true, although a proportion of patients suffering from chorion-epitheliomata—a very primitive type—are still living for quite a long time.

Undoubtedly quite a few radiotherapists conduct a chemotherapy and hormone clinic with their colleagues, and it is to them that this letter is directed. Why wait for the inevitable recurrence—not rarely sudden and often very rapid in growth—after cytotoxic drugs? At the moment there is under my care a patient who had very advanced ovarian carcinoma which was completely resolved by thiotepa (triethylene thiophosphoramide) with support for the bone marrow by "durabolin" (19-norandrostenolone phenylpropionate). When first seen the poor general condition did not permit radical irradiation. Moreover, the presence of large masses meant that the centres of those masses were probably deficient in oxygen and therefore unlikely to be sufficiently radiosensitive to be readily permanently cured. Realizing that recurrence was inevitable a radical course of irradiation was given when the patient was perfectly fit. She is now very well. The duration of survival will be interesting.

One thing can definitely be said about cytotoxic drugs, that although in the main they are still far from curative a proportion of patients may be rendered more amenable to radical radiotherapy and so be given a chance of permanent cure. It would appear likely that cytotoxic drugs, far from being a competitor to radiotherapy, may well prove its handmaiden and extend its scope. Such is the purpose of the combined clinic which we run at this hospital.[2]

Most of us are only too well aware of the equally dramatic disappearance and recurrence of Hodgkin's disease following nitrogen mustard. We might do well to bear in mind the view of that prominent American expert, Dr. Sidney Farber, to the effect that it might be more advantageous to re-explore some of the old remedies properly rather than continually try new ones inadequately. There is little doubt that, as the results of radiotherapy have improved by prolonging the overall treatment times, it is possible that cytotoxic drugs may similarly be better applied and so yield better dividends. Possibly nitrogen mustard may come within this category. Future attention should surely be directed towards tumours other than the reticuloses, which are often very radiosensitive and free of disease for many years. It is generally held to be quite wrong to use cytotoxic drugs for limited disease which can possibly be treated by radiation. Publication of clinical trials of reticuloses treated by cytotoxic drugs is now hardly advantageous.—I am, etc.,

ANTHONY GREEN.

Radiotherapy Department,
Royal Northern Hospital.

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Home-made Wine and Lead-poisoning

Sir,—I was interested in the note by Drs. C. Rickwood Lane and A. Lawrence (October 7, p. 939) on the risks of lead-poisoning from wine made in bread-crocks.

My attention was drawn to this in 1930 in a case where five gallons (22.5 litres) of parsnip wine had undergone its first three-week fermentation in a glazed earthenware bread-crock before being transferred to a barrel. At the time there had been cases reported in the newspapers of lead-poisoning in Devonshire following the drinking of wine so made, and I gave a warning of the risks. This was treated lightly till an analyst's report showed the presence of 11 parts per million of lead, on receipt of which, followed by warnings as to the late results of lead-poisoning, the wine was sorrowfully poured down the drain.

As the authors have pointed out, these bread-crocks have an internal lead glaze, and acid fruit or vegetable juices dissolve this. The strictly correct method is to use oak half-tubs for the early fermentation.

Not all glazes of earthenware cooking vessels are harmless (which is the reason for genuine French terrines being recommended), and acid fruit and vegetable juices can dissolve these glazes.—I am, etc.,

Southport, Lancs. A. N. M. Davidson.

Sir,—The case of lead-poisoning described by Drs. C. Rickwood Lane and A. Lawrence (October 7, p. 939) is of interest. Inhalation in the manufacture of lead glaze for pottery or tile is a known hazard, but trouble from the ingestion of small amounts is less common. In view of the widespread use of lead-glazed articles in the past, is it true—in the statistical sense—to suggest they constitute a dangerous hazard ? It seems reasonable to suggest that these odd cases are not a normal reaction to the ingestion of lead but indicate an unusual susceptibility.

Acute lead colic can be mistaken for an abdominal emergency. The intravenous injection of calcium gluconate may cause an immediate relief of pain and relaxation so that the exclusion of any condition requiring urgent surgical treatment is a simple matter. I have seen a particularly severe case of lead colic in a surgical ward in which the relief from this procedure was so great that the patient fell asleep before the needle was withdrawn. Indeed, if I had a rather larger experience than of only four such cases I might be tempted to describe this test as " diagnostic."—I am, etc.,

Fleet, Hants. A. L. Leigh Silver.

Endomyocardial Fibrosis and G6PD-Deficiency

Sir, — Deficiency of glucose-6-phosphate dehydrogenase (G6PD) in red blood cells has been demonstrated in 10 to 15% of the indigenous population of Uganda.[1-3] It has been postulated that the high incidence of G6PD-deficiency is due to a protective action against malaria,[1 2] which is one of the chief causes of childhood mortality in East Africa. The enzyme-deficiency trait remains common in malarious areas even though it predisposes to haemolysis under certain conditions—for example, on exhibition of therapeutic doses of antimalarial 8-amino-quinolines and certain other drugs.

In an attempt to relate diseases other than haemolytic anaemia to G6PD-deficiency, 20 patients with typical clinical evidence of endomyocardial fibrosis were tested for the enzyme defect. Endomyocardial fibrosis is a common cause of heart disease in Uganda. Its aetiology is at present unknown. For further information on endomyocardial fibrosis the reader is referred to accounts given elsewhere.[4 5] A modification of Motulsky's screening test[6] was used. This gave a normal result in all 20 patients.

Such a small series does not enable a firm conclusion to be drawn. The suggestion that seems warranted is that endomyocardial fibrosis does not appear to be a disease caused by G6PD-deficiency.—We are, etc.,

Department of Medicine, Makerere College, Uganda. K. Somers. F. Lothe.

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Red-cell Aplasia in Marasmus and Kwashiorkor

Sir,—I was very much surprised to read the following statement made by the well-known medical-research team, Drs. Henry Foy, Athena Kondi, and Lorna Macdougall (April 1, p. 937): " So far selective red-cell aplasia has not been reported as a complication of marasmus and kwashiorkor, perhaps because critical haematological work and bone-marrow cytology have not been extensively done in these conditions, and serial bone-marrow punctures are not commonly performed on small infants."

During the last eight years about 3,000 bone-marrow punctures were performed in more than 2,000 children ranging from newborn babies to 12-year-old children with various blood diseases in the paediatric department of the Medical School, University of Indonesia, in Djakarta. Serial bone-marrow and blood studies were done in more than 250 children with kwashiorkor. Results of these last studies were reported in at least four international medical journals[1-6] and at four international congresses.[7-10]

From clinical and haematological studies of 150 cases of kwashiorkor[5] the following conclusions were made concerning the pathogenesis of the anaemia in kwashiorkor: (1) Hypoplastic or aplastic anaemia was found in almost half of the cases, the main criteria for this anaemia being decrease of erythroblasts in the bone marrow, high myeloid–erythroid ratio, decreased number of reticulocytes, and resistance to any treatment. (2) Hypochromic anaemia was found in 31% of the cases probably caused by iron deficiency. (3) Megaloblastic anaemia was found in 13 cases. The finding of giant stab cells in 78 out of 150 cases indicated that there were probably more cases of folic-acid deficiency than indicated by the number of megaloblastic anaemias. (4) The last group consisted of cases with active normoblastic anaemia and which did not react to iron or folic-acid treatment. In another study of 186 cases of erythroblastopenias (pure red cell aplasia)[6 10] three groups could be clearly distinguished: (1) Twenty cases of acute erythroblastopenia, characterized by a sudden drop in the haemoglobin concentration of the blood and the number of reticulocytes, accompanied by the disappearance of erythroblasts from the bone marrow and findings of giant proerythroblasts in the marrow. (2) Twenty-five cases of subacute erythro-

blastopenia without giant erythroblasts in the bone-marrow. (3) The remaining cases were subchronic or chronic erythroblastopenias, mostly found in children with malnutrition.—I am, etc.,

Paediatric Department, University of Indonesia, Djakarta, Indonesia. L. K. Kho.

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Electronic Recording Systems

Sir,—

"We live in deeds, not years; in thoughts, not breaths; "In feelings, not in figures on a dial."

The evocative article by Dr. G. E. Godber, Chief Medical Officer, Ministry of Health (September 30, p. 843), on trends in specialization prompts me to write, in strong support, this plea for the more extended use in British hospitals of the new electronic devices which are now available, and in particular my advocacy is for the recording of observations by this means on the surgical-shock patient of near-irreversible severity.

Temperature, pulse, and respiration rates can be, with this method, readily visualized by the attendant, without dissipation of nurse-hours and with no disturbance of the sick subject. In effect this would largely overcome the disadvantages of the difficult supervision by the night nurse, from a centralized station, in the increasingly popular design of sectionalized wards. Advanced here, moreover, is the use of the electronic technique of recording continuous blood-pressure readings. Every traumatic surgeon of experience is familiar with, and indeed is disquieted by, the picture of the white-faced victim of injury, wincing with the pain and disturbance of the repeated bellows-pumping attendant on the employment of the standard apparatus; such intermittent resistances to cardiac output are inevitably harmful to the near-irreversible case.

If there be employed the intra-aortic method of plasma infusion, in which is used the specially "stepped" needle, designed by M. B. Conlon, inserted in the left lumbar region, as a prelude to pressurized administration, then the *vis a tergo* effect on the coronary arteries, thus perfused, restores the fluttering action of cardiac output; in addition, the increase of kidney tension, promoted through the renal arteries, obviates the risk of tubular suppression of urine. The manœuvre can be readily effected, with no postural disturbance, if the patient be semi-prone on the type of combined casualty trolley and table, with lateral support, designed by Mr. A. M. Murray. At the termination of this immediate plasma infusion by minimal force the connexions can be changed and the blood-pressure curves thus recorded through the medium of the Cardirex machine, as supplied by Siemens, in synchronization with the E.C.G.

If the use of morphine be entirely avoided, but these methods be combined with the selective employment of drugs affecting the adrenergic nerve fibres and other ganglion-blocking agents, epitomized in masterly fashion by Professor J. H. Burn (June 10, p. 1623), then the poetic aphorism quoted above can be re-read as a medical anachronism.—I am, etc.,

Grimsby, Lincs. Daniel Lamont.

Post-operative Urinary-tract Infection

Sir,—Dr. L. Iffy (September 23, p. 829) thinks that the belief of most British surgeons about the superiority of the indwelling catheter over repeated post-operative catheterization is a grave mistake. It would seem that Dr. Iffy is even more mistaken in blaming infection on the indwelling catheter without giving any consideration to the type of catheter or the method of drainage—matters which were very well summarized in your excellent leading article of August 26 (p. 571).

A large-bore rubber catheter draining into an open bottle will almost inevitably give rise to infection, but with closed drainage through a fine Gibbon catheter attached to a sterile receptacle urine may remain sterile for periods of up to six weeks. Such drainage is greatly to be preferred to the serious hazards and discomforts of intermittent catheterization, however carefully done.—I am, etc.,

Dublin. Anthony Walsh.

Apnoea, Hypertension, and Conjunctival Oedema

Sir,—Once again—as in the recent exchange of views on vulval states—your correspondence columns have proved invaluable for discussing the case for which Mr. E. C. Wood and Dr. T. A. Boliston (July 22, p. 217) have sought an explanation. Their patient, who to all intents and purposes was an overweight primipara, had by the 35th week gained 34 lb. (15.4 kg.), a very large amount for that period, and also showed other signs of toxaemia in the slight oedema of her ankles and her blood-pressure of 140/85.

Some further factors need to be taken into account: her section and, accompanying it, the apnoea, and a blood loss severe enough to increase her pulse rate to 140. Additionally ergometrine was injected intravenously, with its oxytocic effect in enhancing the utero-renal reflex, evidence of which had already appeared in her slight pre-eclampsia. As a result of all these stimuli, which will be shown to provoke renal ischaemia, the patient dramatically increased her blood-pressure to 210/130, showed protein and casts, with R.B.C., in her urine, and extension of oedema to the conjunctivae, and was flushed, signs all explicable by the renal ischaemic change now further augmented.

Subsequent contributors (August 12, p. 455, and August 19, p. 522) have noted that carbon-dioxide retention has provoked severe hypertension, and in one case muscular twitchings such as precede convulsions and a reduction of these signs by the use of "apresoline" (hydrallazine), a therapeutic agent shown by Gaunt and Renzi[1] to overcome renal ischaemia and to relieve eclampsia produced experimentally thereby.

The *dramatic elevation* of B.P. and the twitchings may be explained on the basis of Byrom's[2] researches. He has shown that these sudden changes in B.P., followed by convulsions, occur in the rat made hypertensive by the Goldblatt clamp on the kidney—signs that equally dramatically abate on removing the clamp and which are simultaneously correlated to the spasm in the cerebral vessels observed through "perspex"-covered trephine openings. Franklin *et al.*[3] have

convincingly shown that experimental asphyxia is responsible for the most profound renal cortical ischaemia, which in every case proves reversible on removing this stimulus—an experiment which would equate with the alleged effects of the carbon-dioxide retention observed, and the recovery therefrom. Furthermore, Jirka *et al.*[4] have provided unquestionable evidence that severe haemorrhage also stimulates renal ischaemia.

Obstetricians must learn to attach considerable importance to the sign of a flushed skin in view of Floyer's[5] recent investigations into the mechanisms of renal hypertension due to renal ischaemia, in which flushing of the skin finds a rational explanation and is a necessary accompaniment.

Recent evidence by Mukherjee[6] suggests that multiple stimuli of renal ischaemia may summate, which further helps in understanding the clinical manifestations in this case, where the stimulation comprised the utero-renal reflex already present, the asphyxial state, the haemorrhage, the trauma of surgery, and possibly the oxytocic effect of ergometrine. To correlate the symptoms with the renal state we have evidence on: (*a*) oedema, provided by Mueller,[7] who by clipping the renal artery effectively produced retention of salt and water; (*b*) hypertension, provided by Goldblatt,[8] whose clip is now historically related to the aetiology of hypertension; (*c*) proteinuria and casts, an expected accompaniment of renal ischaemia, the former accounted for by Hermann[9] by the increased pore-size of the glomerular vessels after ischaemia; (*d*) the fits (expressed as twitchings in the case reported by Dr. J. L. Webster (August 19, p. 522)), provided by Byrom[2] and already referred to. In view of the wealth of evidence in the literature, it is hard to understand why no obstetrician has drawn attention to this most obvious underlying state of renal ischaemia, which, after all, is his especial province.—I am, etc.,

Worthing, Sussex. JOHN SOPHIAN.

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Nuclear War

SIR,—In general, doctors do not concern themselves with political, social, national, or international problems or crises. That is why the medical profession as a whole shows no apparent concern about a potential impending catastrophe such as the threatening nuclear war and all its consequences to mankind.

I agree wholeheartedly with the spirit and substance of the appeal by Dr. A. A. Clark and others (October 7, p. 964) for a world-wide expression by doctors of concern and protest at the possible destruction of humanity by nuclear weapons.—I am, etc.,

Ilford, Middlesex. R. G. S. HOWE.

SIR,—Once again history has come from the banks of Loch Lomond. Seventeen doctors from Dunbartonshire have come together to declare "that the defence of any principle, either political or religious, does not warrant the total destruction of humanity" (October 8, p. 964).

This declaration will meet with wide acceptance. Some may join in statistical argument as to whether "total destruction" is accurate to the final decimal. My own reaction is to wonder how we as doctors—in the past a dedicated community—can canalize such thoughts constructively. We know that the possibility of nuclear war starting by accident increases with each passing year. In this age preventive medicine demands complete and universal disarmament. We as doctors would serve the nation well when we remind our people and our government of such obvious truth.—I am, etc.,

Edinburgh 9. J. LIPETZ.

SIR,—The letter from 17 Dunbartonshire doctors (October 7, p. 264) gives expression to the increasing concern which many in the profession feel regarding the danger of nuclear war. Our medical training and traditionally humanitarian outlook impose on us an additional responsibility in present circumstances which is difficult to express individually and more difficult still to implement. But there has never existed a more serious threat to life and health than nuclear weapons, both in their short-term and long-term effects, and our interest in preventive medicine alone would seem to call for a vigorous and united protest to all governments who are prepared to use such weapons. The effect would not be inconsiderable, especially if the profession in other countries could see their way to doing likewise.

Perhaps the Association could call an early meeting to discuss what can be done.—I am, etc.,

Clare Hall Hospital, South Mimms, Herts. NORMAN MACDONALD.

SIR,—We wish to express our solidarity with our colleagues in Dunbartonshire, Scotland, in their protest against nuclear weapons made in your issue of October 7 (p. 964). We likewise call upon the profession to register a protest against the continued existence of weapons of mass destruction which threaten the survival of humanity.—We are, etc.,

MARY BARBER.
E. G. L. BYWATERS.
IRENE DATT.
NAOMI DATTA.
JOHN DALY.
ALLAN DIXON.
RUTH HASLAM.
T. HAZRA.
ROBERT HOLLISTER.
DAVID HULL.
M. KOCHHAR.
V. A. KUMOJI.
D. LILARAM.
GRAHAM MCCARTHY.
CHRISTOPHER PALLIS.
J. PAYNE.
MALCOLM SEGALL.
D. R. SMITH.
C. VAS.
L. VERMA.
IAN WOOTON.

Hammersmith Hospital, London W.12.

SIR,—I send whole-hearted support for the letter (October 7, p. 964) under "Nuclear War," and signed by 17 doctors in Dunbartonshire.—I am, etc.,

Harrow, Middlesex. JOAN HOUSEMAN.

SIR,—I wish to associate myself with the sentiments and opinions expressed in the letter (October 7, p. 964) from 17 medical practitioners in Dunbartonshire.—I I am, etc.,

Colchester. NORA M. JOHNS.

Codeine for Bronchitis

Sir,—In your leading article on bronchitis (October 14, p. 1004) you state that "syrup of codeine 5–10 ml. or tablets ½–1 gr. (30–60 mg.) is usually effective" in dealing with the useless cough of bronchitis. Linctus codein., however, you state to be almost useless, since it contains so little of the drug. I find that the *British National Formulary, 1960*, states that 60 min. (3.6 ml.) of the linctus contains 45 min. (2.7 ml.) of the syrup. Two normal teaspoonfuls thus contain 90 min. (5.3 ml.). Your statement must therefore be disputed.—I am, etc.,

Birkenhead, Cheshire. Fred Owers.

Aspirin Anonymous

Sir,—Dr. D. B. Davies's letter (September 30, p. 896) is certainly of great interest and importance. I have recently encountered a similar patient who was an asthmatic and who knew he was sensitive to aspirin and who naturally wished to avoid salicylates. In this case the patient was a medically qualified doctor. On a recent occasion he took a powder known as "rybronsol" for the relief of his asthmatic symptoms, and immediately became cyanosed and unconscious. This preparation contains phenazone acetylsalicylate. In view of the fact that a significant proportion of asthmatics are hypersensitive to aspirin, it is surprising to find salicylates included in a therapeutic agent recommended for the treatment of this complaint.—I am, etc.,

Harefield Hospital, Middlesex. L. E. Houghton.

Best Time for Lectures?

Sir,—Many of us will support the plea of Dr. M. Sifman (October 7, p. 964) for a change of time to the afternoon for the B.M.A. clinical meetings. With varying off-duty periods any evening will be wrong for some, but the great majority would be able to fit in an early afternoon session.—I am, etc.,

Surbiton, Surrey. L. P. J. Wright.

POINTS FROM LETTERS

Lignocaine with Adrenaline

Dr. A. J. Jouhar (Medical Adviser, Duncan, Flockhart and Co. Ltd., Edinburgh) writes: In the absence of a 0.5% lignocaine with 1:200,000 adrenaline, one can readily obtain the mixture by using *x* ml. 0.5% plain lignocaine + *x* ml. 0.5% lignocaine with adrenaline 1:100,000. However, I am glad to announce that this company is now marketing . . . the following additions to its range of "duncaine" brand of lignocaine: 0.5% duncaine with adrenaline 1:200.000 in 20 ml., 50 ml., and 250 ml. containers; 1% duncaine with adrenaline 1:200.000 in 20 ml. and 50 ml. containers; and 2% duncaine with adrenaline 1:200,000 in 20 ml. containers.

Mr. Denis S. Sissons (Home Sales Manager, Pharmaceutical Manufacturing Company, Epsom, Surrey) writes: We would like to advise those who may be interested that "xylotox" brand lignocaine hydrochloride local anaesthetic solutions have been available for many years in 0.5%, 1%, and 2% strengths and included in the range is a 0.5% solution with adrenaline 1:200.000 available in 20 ml. and 50 ml. bottles as well as larger packs.

Obituary

LAMBERT C. ROGERS, C.B.E., M.D., M.Ch., M.Sc. F.R.C.S., F.R.C.S.Ed., F.R.A.C.S., F.A.C.S.

By the sudden death of Professor Lambert Rogers on October 10 at the age of 64 the medical profession lost a distinguished surgeon, Wales lost her professor of surgery, and the world has lost a man of great sincerity, charm, and kindliness.

Lambert Rogers was born in Melbourne, Australia, on April 8, 1897, but he spent well over half of his life in Wales, the land of his adoption, and in Cardiff, where he occupied the chair of surgery with great distinction for 26 years. School days were passed in Melbourne, but Lambert Rogers received his medical education at the Middlesex Hospital in London. He entered the medical school there during the first world war, and his studies were twice interrupted by periods of war service—first in the Australian Naval Transport Service, in which he remained until 1917, and then, after a brief return to medical studies, as a surgeon probationer in the Royal Naval Volunteer Reserve. In spite of these interruptions his early student days were full of promise and he gained prizes in anatomy, physiology, and histology. The war over, he returned to the Middlesex, qualified in 1920, and was awarded a certificate of distinction as a prosector in anatomy in the University of London. After working as Sir John Bland-Sutton's house-surgeon at his teaching hospital he spent the next few years in acquiring a very varied experience as ship surgeon, in general practice, and in New York.

[*Elliott and Fry, Ltd.*

His real life work began in 1926, when he was appointed the first full-time assistant in the surgical unit of the Welsh National School of Medicine in the Cardiff Royal Infirmary. Here he worked under the first professor of surgery in the school, Professor A. W. Sheen, and under the guidance of such a stimulating personality he began to develop those branches of surgery which became his lifelong interest. In 1929 he was appointed the first full-time senior assistant in the surgical unit and shortly after was made assistant director of the unit. In 1928 he graduated M.Sc.(Wales). In those early days Lambert Rogers maintained an active interest in anatomy and physiology and worked as demonstrator in the department of anatomy and carried out animal research work on periarterial sympathectomy with Professor A. Hemingway in the physiology department, as well as contributing several articles to the journals on anatomical subjects.

He also became interested in the two branches of surgery which continued to engage his attention throughout his life. In Cardiff he found himself in an area of endemic goitre, and he was not slow to take advantage of the opportunity this offered to study the condition and to make himself the master he became in the surgical treatment of goitre and thyrotoxicosis. In the days before antithyroid drugs or even iodine premedication the operation of partial thyroidectomy in a severely thyrotoxic patient was a major hazard and carried a formidable mortality. Lambert Rogers met the problem by carrying out staged procedures of thyroid-artery ligations under local anaesthesia, and he contributed papers on this method and also on the anatomy of the thyroid vessels. In his study of thyroid disease he was closely associated with Dr. Ivor Davies, then an assistant

on the medical unit. The other branch of surgery which attracted him was neurosurgery, then in its infancy, and he was successful in establishing this specialty in Cardiff, and spent much time in developing the techniques of neurosurgical diagnosis and treatment, inventing and developing new instruments for craniotomy, and applying new diagnostic measures as they were introduced. He became a close friend of some of the pioneers of this branch of surgery, including Harvey Cushing himself, and later he became a vice-president of the Society of British Neurological Surgeons. It was a source of great satisfaction to him when one of his old pupils was appointed neurosurgeon to the United Cardiff Hospitals after the second world war: Professor Rogers then progressively gave up the intracranial aspects of neurosurgery, but he retained a keen interest in the surgery of the spine and spinal cord, and in particular the surgery of spinal tumours, in which he accumulated an unrivalled experience and became the acknowledged authority in Great Britain.

In 1934 Lambert Rogers was appointed a Hunterian Professor of the Royal College of Surgeons and in the same year he left Cardiff to spend a year as reader in surgery at the British Postgraduate Medical School at Hammersmith. Here he became associated with Professor Grey Turner, who then occupied the chair of surgery and for whom he came to have a very high regard. The two men became close friends, and the last public lecture which Professor Lambert Rogers delivered was a few weeks ago at the Congress of the International Society of Surgery in Dublin, where he gave the first Grey Turner Memorial Lecture. He was also appointed a vice-president of the International Society.

In 1935 Lambert Rogers returned to Cardiff to succeed A. W. Sheen in the chair of surgery and as director of the surgical unit, continuing in this appointment until his death. Under his stimulating leadership and wise guidance the surgical unit has flourished and many surgeons who received their early surgical training there have achieved distinction. He was always eager to encourage young surgeons who worked with him, and many old students consulted him about their careers. His advice was never sought in vain and was always given with great thought and care and with complete honesty. In the Welsh National School of Medicine it has always been the rule that all students do three months of their surgical dressership in the surgical unit, and in the 26 years that Professor Rogers occupied the chair of surgery more than a thousand medical students must have come under his direct influence in this way, and it is a testimony to the effectiveness of this influence that so many of them always sought him out whenever they returned to Cardiff in later years.

Professor Rogers was well known too as an examiner in surgery in several medical schools as well as on the Court of Examiners of the Royal College of Surgeons. Here he not only examined for the Conjoint Diploma and Final Fellowship, but also became an examiner in anatomy in the Primary Fellowship not only in this country but also in Cairo and Colombo. He served for many years as a member of the Council of the Royal College of Surgeons, becoming in due course a vice-president of the College. He was also at different times president of the Association of Surgeons of Great Britain and Ireland and of the Welsh Surgical Society, which he founded in 1953. He was president of the Section of Surgery of the Royal Society of Medicine during its last session.

From the days of the first world war Lambert Rogers had always had a love for the sea and for ships, and it was no surprise when in the second world war he again volunteered to join the Royal Navy and served with distinction as a surgeon captain in Great Britain and the Pacific. He received the V.R.D. in 1946.

His international reputation is attested by the long list of honorary degrees and diplomas which were bestowed upon him. None of them gave him more pleasure than the M.D. conferred upon him in Melbourne, his birthplace, during a honeymoon trip to Australia after his marriage in 1952 to Barbara Ainsley. He was appointed C.B.E. in 1958, and only a few weeks ago the National University of Ireland conferred on him the honorary degree of M.Ch.

Professor Lambert Rogers had surgical friends all over the world and he was known and respected among surgeons everywhere. In spite of his many surgical appointments and busy life, it was characteristic of the man that he was always ready to answer requests for help from other medical and charitable organizations, and every office that he accepted received a full share of his time and enthusiasm, for he was not content to be merely a figurehead. Thus for many years he was county medical officer for the Glamorgan Branch of the British Red Cross Society, and in that capacity took a full part not only in the committee and administrative work of the society but also in the organizing of first-aid teaching and competitions. He was also for many years on the executive committee of the Cardiff Division of the British Medical Association, and in spite of ill-health he accepted the presidency of the South Wales Branch of the B.M.A. in the year before his death.

Apart from his achievements as a surgeon, Lambert Rogers's outstanding characteristics were those of kindliness and courtesy. He was always quick to praise and slow to criticize, and, while he was a very shrewd judge of character and capability in others, he always was ready to see the best in other people. He was a man of strong Christian convictions, and for him religion was not something added on but an integral part of life. He interested himself in many Christian causes, and while he never paraded his religion he never sought to hide what was so much a part of his life. He was a Churchman by conviction, and whenever he was in Cardiff at the week-end it was his custom to read the lessons at the morning service on Sundays at the Royal Infirmary Chapel. He will be sadly missed by many who never knew him as a surgeon, but who valued his friendship and who were helped by his life and by his example.—A. S. A.

J. W. T. T. writes: The sudden and unexpected death of Lambert Rogers has been a great shock to his Cardiff colleagues and is a sad loss to the hospital and medical school in whose interests he had worked so faithfully and well for some 36 years. He was devoted to his work, and his reputation as a surgeon, a research worker, and a teacher was very high. He also took his full part in the committee work of the institutions to which he belonged, and when he spoke in committee his remarks were always sincere and based on sound judgment and knowledge. Many of us had listened to his proposing a vote of thanks after a presidential address at the Cardiff Medical Society the night that he died. As always his words were delightfully phrased and well-delivered, and none of us had any thought that this was to be his last public occasion. He was stricken fatally ill on his way home from the address.

In every sense a true friend, he was always ready to help with friendly and sound advice. He was very loyal to his colleagues and to his old teachers. So often he would refer with great respect and affection to Bland-Sutton, Gordon-Taylor, and Grey Turner—all great men whom he held in such high esteem.

Lambert was one who liked to take great care in everything he did. In his surgical technique he was meticulous, in his writings painstaking. He would go to much trouble to introduce an apt quotation or to produce some historical reference bearing on the subject. He took great interest in the history of medicine, and on many occasions we have heard him discuss historical medical incidents, speculating and debating on the true nature of things in the light of modern knowledge. In all this, as in his surgery, he was a master.

He was indeed one who had many friends, and had endeared himself to us all by his kindly gentle nature, his staunch support for all that was right, and his keen interest in the affairs of his colleagues and his readiness to express his appreciation of what they did. He will be missed in Cardiff, and the sadness we feel is shared in that large circle in which he moved throughout the country and indeed

throughout the world. We sympathize most deeply with his widow and the family which he leaves.

Professor Gilbert I. Strachan writes: I am writing about Lambert Rogers not so much as a surgeon of international reputation but mainly as a colleague of many years' standing on the professorial staff of the Welsh National School of Medicine in the University of Wales. He was a man of high academic ideals which he expressed with firmness and if necessary with force as occasion required. His main interests were the dignity of his professorial chair, the efficiency of his department, and, in particular, the affairs of the Welsh National School of Medicine, to which he rendered such outstanding services and which owes him an enormous debt. Among the most important of his other interests was his work on the council of the Royal College of Surgeons, where he served for sixteen years; he had not long completed his term of office as a vice-president. Again, he was a keen B.M.A. man and he had been chairman of the Cardiff Division, and only last year was president of the South Wales and Monmouthshire Branch.

Others will write about his considerable surgical achievements; here I would wish to record my deep appreciation of his loyalty and of the friendship that existed between us for many years. It was indeed a pleasure to know him and to work with him, and his tragic and unexpected death removes a figure from among us in South Wales that will not easily be replaced.

Deep sympathy goes out to his widow and young daughter as well as to his stepson, to whom he was deeply attached.'

A. J. K. DREW, M.R.C.S., L.R.C.P.

Dr. A. J. K. Drew, who was formerly in practice in Ramsgate, died suddenly at his home in Tunbridge Wells on September 7. He was 72 years of age.

Albert John Kingman Drew was born in Wareham, Dorset, on March 19, 1889, the son of John Albert Drew, J.P. Educated at Eastbourne College, he qualified from Guy's Hospital Medical School in 1915. Being pronounced medically unfit for active service, he gained much surgical experience at the Bolingbroke Hospital, Wandsworth, the Portsmouth General Hospital, and the Royal Surrey County Hospital, Guildford, as well as at the Golden Square Ear, Nose and Throat Hospital in London. The greater part of his working life was spent in practice in Ramsgate. Appointed surgeon to the Ramsgate General Hospital in 1922, he served that hospital faithfully until 1954, for most of the time as senior surgeon. He was also for some years surgeon obstetrician to the maternity department and continued in charge of the antenatal department until 1958. During the second world war he was sent under the Emergency Medical Service to the Lewisham and Barking Hospitals, being in many of the air raids in the areas.

One of his hobbies was mountain climbing, mostly on snow and ice in Switzerland. He was also a member of the Magic Circle in London and was often at its meetings up to the last: he used to give many amusing turns at both adult and children's parties. Although at times somewhat hesitant in speech he was never hesitant while operating. One of his anaesthetists remarked that what his mind had decided should be done his beautiful hands did swiftly and neatly.

Dr. Drew is held in affectionate remembrance by his many patients at Ramsgate for his unfailing kindness and patience, as also by his colleagues. Much sympathy is felt for his two younger sisters and for his many close friends, all of whom miss him greatly.—S. C. S.

ISRAEL HOLMGREN, M.D.

Dr. Israel Holmgren, the doyen of physicians in Stockholm, died on September 20 at the age of 90. Formerly professor of medicine at the Karolinska Institutet and director of the Seraphim Hospital, he edited *Acta Medica Scandinavica* for 41 years.

Israel Holmgren was born in Uppsala and graduated in medicine at the Karolinska Institutet. He quickly distinguished himself in the academic and clinical appointments to which he was elected, and from 1925 to 1933 he was a member of the Swedish Parliament, belonging to the Liberal Party and being well known for his opposition to totalitarian forms of government.

In the early part of his career he carried out useful biochemical research in such subjects as the analysis of gastric juice, and later he wrote books on tuberculosis and on thyrotoxicosis. But his main literary work was his editorship of *Acta Medica Scandinavica*, which he saw grow into the influential journal it is to-day. In a farewell note published in that journal in 1957 he wrote: "I feel proud that during the 41 years I have edited and led its fortunes, *Acta Medica Scandinavica* has grown into a journal that has spread literally to all the countries of the globe. I draw the conclusion that the medical profession has found it of value and feel grateful for the appreciation."

A memorial service for Sir Bentley Purchase will be held in the Temple Church, London E.C.4 (by kind permission of the Master and Benchers of the Inner and Middle Temples), at 4.30 p.m. on Tuesday, October 24.

Vital Statistics

Poliomyelitis at Hull

The outbreak of acute poliomyelitis at Hull is the first in Great Britain to be combated by the administration of a Sabin oral vaccine containing live attenuated virus. The strain used is type 2 on the principle of blocking colonization of the gut by the epidemic type 1 strain.

We are indebted to Dr. A. Hutchison, Medical Officer of Health to Kingston upon Hull, for the following information: The first case was notified on October 4, and up to October 17 46 cases had been notified. Five more were under observation. Twenty-one of the 46 patients are under 5 years old, 11 are from 5 to 15, 10 are from 16 to 28, and 4 are over 28. Only 2 of the children (both in the 5–15 age group) have had a full course of injections of Salk vaccine, but 12 others have had either one or two injections. There had been no deaths up to October 17, and no household had been reported with more than one case. (See leading article on page 1072.)

Infectious Diseases

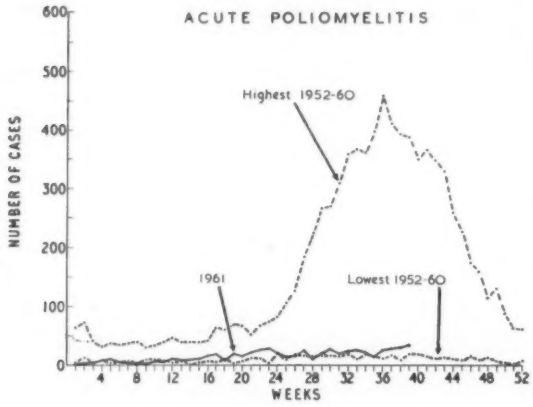
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

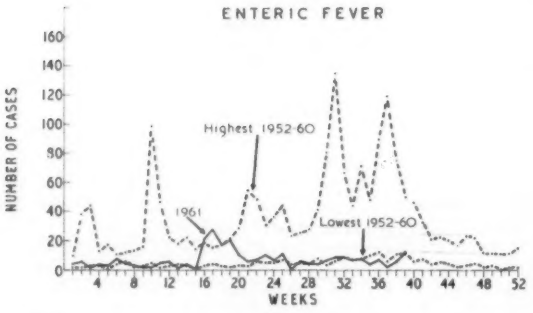
	Week Ending Sept. 30	Week Ending Oct. 7
Dysentery		
Lancashire	99	**77**
Yorkshire East Riding	10	**18**
Yorkshire West Riding	44	**70**
Glasgow	108	**127**
Edinburgh	24	**38**
Dundee	23	**27**
Acute poliomyelitis		
Lancashire	18	**12**
Bolton C.B.	1	**4**
Yorkshire East Riding	2	**9**
Kingston upon Hull C.B.	2	**9**
Yorkshire West Riding	2	**7**
Sheffield C.B.	2	**3**

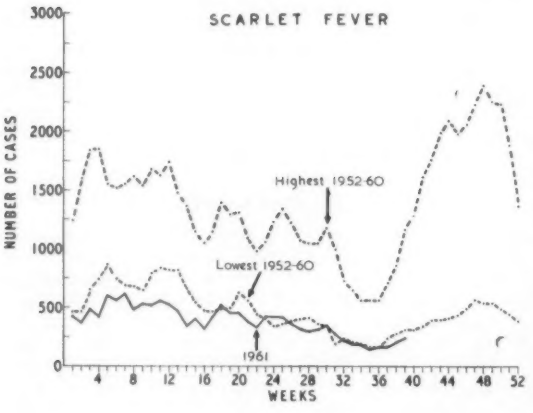
Graphs of Infectious Diseases

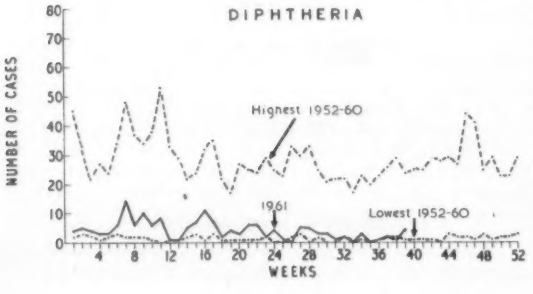
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales.

Highest and lowest figures reported in each week during the years 1952–60 are shown thus - - - - -, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 30** (No. 39) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	4	1	1	0		4	0	0	0	3
Dysentery ..	309	21	175	8	13	477	64	185	6	
Encephalitis, acute	4	1		0		1	0		0	
Enteric fever:										
Typhoid ..	3	0	2	0		5	3	2	1	
Paratyphoid ..	9	1	3(B)	0		6	0	1	1	
Food-poisoning ..	283	18	38	1		287	29	20	9	
Infective enteritis or diarrhoea under 2 years				12	28				18	33
Measles*	985	36	26	34	53	1,891	86	59	4	7
Meningococcal infection	12	1	1	0		19	3	7	0	1
Ophthalmia neonatorum	28	4	4	0		24	1	1	0	
Pneumonia† ..	91	9	75	0		175	9	114	4	1
Poliomyelitis, acute:										
Paralytic ..	28	2	0	1	3	12	6	0	0	6
Non-paralytic ..	6	0	1			6	1	0		
Puerperal fever§ ..	156	24	15	1		153	31	9	0	
Scarlet fever ..	240	19	38	12	8	305	15	45		22
Tuberculosis:										
Respiratory ..	365	25	51	12		386	50	50	15	
Non-respiratory	4	0	11	2		50	4	11	3	
Whooping-cough	249	20	32	7	7	10	117	101	9	20

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		1			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	2	1	0	8	1	1	0	0
Influenza	3	0	0	0	1	7	0	1	1	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	328	24	12	11	3	431	46	16	19	5
Poliomyelitis, acute	0	0		0	0	0	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	45	0	2	1	6	61	3	3	2	3
Non-respiratory		0		0	0		0	0	0	0
Whooping-cough	3	0	0	0	0	0	0	0	0	0
Deaths 0–1 year ..	289	38	32	5	13	280	27	21	7	11
Deaths (excluding stillbirths) ..	8,356	667	506	103	150	9,026	749	605	133	124
LIVE BIRTHS .	15,921	1313	1065	267	331	15,478	1327	1035	290	300
STILLBIRTHS ..	293	18	22			269	18	18		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

World Medical Association

Dr. Ian Grant, Chairman of the Council of the B.M.A., was elected a member of the Council of the World Medical Association by the General Assembly at its recent meeting in Rio de Janeiro.

New London Rehabilitation Centre for Disabled

A social and rehabilitation centre specially designed for handicapped people has been built by the London County Council near Victoria Station. About 250 handicapped people attend the centre, which has a full range of craft rooms, every week. A fully equipped household unit with a model kitchen has been provided for disabled housewives, and courses for the newly blind are held with classes ranging from mobility training to clay modelling, carpentry, and basketwork. Training is given in Braille and Moon type, in Braille shorthand and typing, and in telephone switchboard operating. The new building also serves as the L.C.C. Welfare Department's West London district office, and on the ground floor is a permanent exhibition of aids for the handicapped and a shop where goods made by the disabled are on sale.

British Hospitals Contributory Schemes Association

In its *Thirteenth Annual Report 1960-61* the British Hospitals Contributory Schemes Association notes that at the end of 1960 there were for the first time over 4,000,000 contributors. Affiliated schemes registered an increase of 56,382 compared with 67,549 in 1959; non-affiliated schemes added 4,923 compared with 1,690 in 1959. The affiliated schemes collected £48,836 more than in 1959 and the non-affiliated £10,930. Attention is again drawn to the disappointingly low average weekly contribution of 3.60d. Charitable distributions totalled £76,547 compared with £75,222 in 1959 and £77,068 in 1958. Since the Health Service started £981,688 has been given for amenities for hospital patients, medical charities, and research.

Bristol Hospitals Fund

The Bristol Hospitals Fund (for medical charities, medical research, and amenities for hospital patients) and the Bristol and West Health and Hospital Services Fund (for providing ancillary and supplementary benefits to those available under the National Health Service) record in their *Reports for 1960* that the contributory income amounted to £57,870, the highest income since 1948. One in every four contributors received benefit for themselves or their dependants, 12,242 claims being settled. The Charitable Appeals Department distributed £3,701 during 1960 for amenities for patients, medical charities, and research—making a total of £42,751 since the National Health Service started. Of this total £8,173 has been given to the Bristol Mobile Physiotherapy Service, and £13,849 to the University of Bristol and Bristol Royal Hospital Cancer Research Funds.

Centres for Radiation Casualties

Liverpool Regional Hospital Board has approved the provision of centres at Liverpool Radium Institute and at Clatterbridge Hospital, Wirral, for treating those affected by accidental radiation. Such accidents might occur in nuclear establishments, industries using radioactive materials, and in experimental or research work with radiographic apparatus.

Malta Branch for Royal Society of Health

A branch of the Royal Society of Health is to be formed in Malta. The Governor of Malta and the Archbishop of Malta have agreed to be patrons of the new branch, the chairman of which is Professor J. Galea, formerly Chief Government Medical Officer.

John Cary House Opened

John Cary House, a new psychiatric unit at Barrow Hospital, Bristol, was recently opened. It used to be a male nurses' hostel, and has been converted to house nine men and 15 women in rooms for one, two, or three patients. It will admit suitable cases of neurosis and psychosis for an average stay of one month, giving an admission rate of around 300 a year. An intensive social and occupational programme will be organized with special emphasis on the social life of the group and on preserving the links between the individual and his home. The new unit has been named after John Cary, a seventeenth-century Bristol citizen whose proposals in 1696 led to the founding of St. Peter's Hospital.

New Director, World Federation for Mental Health

Dr. François Cloutier, senior consultant to Queen Mary's Veterans Hospital, Montreal, has been appointed director of the World Federation for Mental Health from January next year. He succeeds Dr. J. R. Rees, who was the first president of the Federation when it was founded in 1948 and has been its director since 1949. Dr. Rees will now act as consultant to the Federation.

Dr. Cloutier, who is 40, holds the B.A. and M.D. of the University of Quebec and diplomas in neurology and psychiatry. He studied ethnology at the Sorbonne and the Musée de l'Homme in Paris in 1952. He is a Fellow of the Royal College of Physicians of Canada and of the American Psychiatric Association.

New Block at Central Middlesex Hospital

A new building housing the Pathology Department and an extension to the Out-patients Department at the Central Middlesex Hospital was opened by Lord Moynihan, the chairman of the North-west Metropolitan Regional Hospital Board, on October 14. The new building, which cost £115,000 to build and £15,833 to equip, is the first stage of a programme of extensions which is to be carried out at the hospital.

"World Directory of Dental Schools"

In Indonesia there is one dentist to every 283,000 (in 1957), in Israel 1 : 1,400, in the United Kingdom 1 : 3,900. These are some of the facts given in the World Health Organization's *World Directory of Dental Schools*—a parallel volume to its *World Directory of Medical Schools*. Each of the 70 countries covered forms the subject of a separate chapter in which are described the administration, conditions of admission, curriculum, and examination procedures of the dental schools, together with details of the regulations governing licence to practise. Certain items of information, such as the number of dental schools and the ratio of registered dentists to population, are tabulated at the head of the chapter. The schools themselves are listed in tables giving the name and address, date of foundation, number of teaching staff, total enrolment, annual admissions, number of graduates, and annual tuition fees. There are two appendixes: one summarizes the obligations which certain States require from their dental graduates, the other lists the basic degrees and diplomas conferred by dental teaching institutions in the 70 countries (Available from H.M.S.O., price £1 5s. Also published in French.)

British Postgraduate Medical Federation

The British Postgraduate Medical Federation's new series of lectures on the "Scientific Basis of Medicine" was inaugurated on October 17 by Lord Cohen of Birkenhead who spoke on ". . . the elements, So mix'd in him, . . ."—a study in human constitution and disease.

Diabetic Research

A donor has offered £1,000 to help research on insulin fat atrophy. Applications describing the proposed project, the qualifications of the investigator, and the support required should be sent to the secretary of the Medical and Scientific Section, the British Diabetic Association, 152 Harley Street, London W.1, by December 1.

Change of Address

The new address of the head office of Birmingham's Public Health Department is Trafalgar House, Paradise Street, Birmingham 1. (Telephone: CENtral 9944.)

COMING EVENTS

Royal Northern Hospital.—Annual scientific exhibition, October 21–28, 10 a.m.–6 p.m., board room of hospital. All doctors and senior medical students welcome.

Association of Industrial Medical Officers.—Meeting, October 27, Royal College of Surgeons, Lincoln's Inn Fields, London W.C.2; October 28, Westminster Hospital, London S.W.1. Details from Honorary Secretary, A.I.M.O., 47 Lincoln's Inn Fields, London W.C.2.

William Mackenzie Lecture. — Professor MEYER-SCHWICKERATH, "The Management of Ocular Tumours," October 27, 5 p.m., hall of Royal Faculty of Physicians and Surgeons, 242 St. Vincent Street, Glasgow.

Fellowship for Freedom in Medicine.—Annual general meeting, October 28, 2.15 p.m., Caxton Hall, Westminster, London S.W.1.

Abortion Law Reform Association.—Annual general meeting, November 1, 6.45 p.m., Conway Hall, Red Lion Square, Holborn, London W.C.1, followed by public meeting at 7.30 p.m. Speakers: Miss JOAN VICKERS M.P., "The Status of Women Commission"; R. S. W. POLLARD, Esq., J.P., "Practical Problems of Getting the Law Amended." Questions and discussion. Admission free.

NEW ISSUES OF SPECIALIST JOURNALS

The Journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH JOURNAL OF OPHTHALMOLOGY

Electrical Potential Across the Isolated Ciliary Body Observed in vitro. D. F. Cole.
Retroiental Decompression for Malignant Glaucoma. A. Stewart Scott and Vernon H. Smith.
Superior Orbital Fissure Syndrome of Uncertain Actiology. A. Mortada.
Juxtapapillary Hamartoma of Retina. B. S. Cardell and M. J. Starbuck.
Surgical Cure of Senile Entropion. W. S. Foulds.
Retinal Pathology After Central Retinal Vein Occlusion. J. Reimer Wolter.
Effect of Sustained-release Diamox on the Intra-ocular Pressure in Man. S. M. Drance and F. Carr.
Reviews.
Notes.

Volume 45, No. 10. (Monthly; £6 annually. With *Ophthalmic Literature* and Index £9.)

BRITISH JOURNAL OF PREVENTIVE AND SOCIAL MEDICINE

Anencephalus in Scotland. R. G. Record.
The Relation Between Smoking Habits and Physique, Respiratory Symptoms, Ventilatory Function, and Radiological Pneumoconiosis Amongst Coal Workers at Three Scottish Collieries. J. R. Ashford, S. Brown, D. P. Duffield, C. S. Smith, and J. W. J. Fay.
Multiple Sclerosis in British Commonwealth Countries in the Southern Hemisphere. E. D. Acheson.
Incidence of Gastric and Duodenal Ulcer in the Royal Navy in 1955. J. H. Baron and R. Vaughan Jones.
Prevalence of the Commoner Ear, Nose and Throat Conditions in the Adult Rural Population of Great Britain. R. Hinchcliffe.
Society for Social Medicine.

Volume 15, No. 3. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 23

MANCHESTER MEDICAL SOCIETY.—(1) SECTION OF ODONTOLOGY: At Lecture Room, Dental Hospital, 4.30 for 5 p.m., Presidential Address by Professor H. G. Radden: Mouth Wounds. (2) SECTION OF GENERAL PRACTICE: At Large Anatomy Theatre, Medical School, Manchester University, 8.30 for 9 p.m., Mr. A. R. Anscombe: Abdominal Pain.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. Brian Ackner: Hypochondriasis.
UNIVERSITY COLLEGE LONDON.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Professor J. N. Davidson, F.R.S.: Biosynthesis of Polynucleotides.

Tuesday, October 24

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. L. Brent, Ph.D.: Some Current Problems in Transplantation Immunity.
KEIGHLEY AND DISTRICT MEDICAL SOCIETY.—At General Hospital, Skipton, 8.30 p.m., Dr. G. Watkinson: Peptic Ulcer.
MANCHESTER MEDICAL SOCIETY.—At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., University Lecture on the History of Medicine, by Mr. W. W. Nicholson: Napoleon and his Doctors.
ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Dr. A. G. W. Whitfield: Pulmonary Fibrosis.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. A. J. M. Reese: Tumours of the Kidney.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Andrew Claye: Disturbances of Sexual Function.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. E. H. Larkin: Drug Treatment in Psychiatry.
WESTMORLAND COUNTY COUNCIL.—At County Hall, Kendal, 4 p.m., Dr. R. H. Seville: Dermatology for Nurses.

Wednesday, October 25

BONE AND TOOTH SOCIETY.—At Institute of Orthopaedics, 4 for 4.30 p.m., symposium: Fluorides. Papers by Dr. G. N. Jenkins, Dr. S. M. Weidmann, Dr. A. M. Bond, and Dr. W. T. C. Berry.
GLASGOW UNIVERSITY: INSTITUTE OF VIROLOGY.—At Lecture Theatre, Department of Pathology, Western Infirmary, Glasgow, 4.30 p.m., Pfizer Lecture in Virology, 1961, by Dr. G. K. Hirst (New York): Animal Virology as a Biological Science.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Professor C. D. Calnan: Physiology of Itching.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. R. V. Gibson: Constrictive Pericarditis and Cardiac Tamponade.
● INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 3 p.m., discussion: Prematurity. Guest speakers: Professor G. Gordon Lennon and Mr. G. H. Bancroft-Livingston.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. H. J. G. Bloom: Radiotherapy.
MANCHESTER MEDICAL SOCIETY: SECTION OF MEDICINE.—At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., Dr. J. N. Walton: Current Concepts of Muscle Disease.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. M. D. Milne: Renal Function Tests.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Arnott Demonstration by Dr. D. H. Tompsett: Casts of the Bronchial Tree (with practical demonstration).
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.—5.15 p.m., Professor J. V. Dacie: Some Aspects of Haemolytic Anaemias.

Thursday, October 26

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF ANAESTHETICS.—8.15 p.m., Dr. H. Rex Marrett: New Technique and a New Machine for Outpatient and Dental Anaesthesia (illustrated by sound film).
BRISTOL UNIVERSITY: DEPARTMENT OF PSYCHIATRY.—At Small Theatre, Queen's Building, University Walk, 8.30 p.m., Professor Martin Roth: Borderland Between Functional and Organic Mental Illness—a Growing Point in Psychiatric Research.
BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. Henry Harris: Transfer of Information from Nucleus to Cytoplasm.
GLASGOW UNIVERSITY: INSTITUTE OF VIROLOGY.—At Lecture Theatre, Department of Pathology, Western Infirmary, Glasgow, 4.30 p.m., Pfizer Lecture in Virology, 1961, by Dr. G. K. Hirst (New York): Virus Neutralization—an Immunological Phenomenon.
HILL END HOSPITAL MEDICAL SOCIETY.—8.30 p.m., speaker, Dr. Richard Asher.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Professor A. W. Grace (New York): Microscopic Pattern of Disintegration of Nuclei in Pemphigus, Contact Dermatitis, and Disseminated Lupus Erythematosus.
LEWISHAM GENERAL HOSPITAL.—5.45 p.m., clinico-pathological conference.
LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. R. C. Nairn: Immunofluorescence in Medicine.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Thomas Vicary Lecture by Sir Clement Price Thomas: Vicary Amongst His Contemporaries.
ROYAL SOCIETY.—10.30 a.m., symposium on Biochemistry and Nutrition to celebrate the centenary of the birth of a former President of the Society, Sir Frederick Gowland Hopkins, O.M. Under the leadership of Professor R. A. Morton, F.R.S.
ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, Queen's College, Dundee, 5 p.m., Dr. H. Lehmann: Modern Developments in the Recognition of Abnormal Haemoglobins.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5.15 p.m., Dr. M. Partridge: postgraduate demonstration in psychiatry.
UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., lunch-hour lecture by Dr. A. S. G. Curtis: Capabilities of a Living Cell.

Friday, October 27

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. Smart: clinical demonstration.
PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields Hospital, 8.30 p.m., clinical evening.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. V. H. Riddell: Unsettled Thyroid Problems; (2) 4 p.m., Professor L. S. Penrose: Mongolism.

Saturday, October 28

ASSOCIATION OF ANAESTHETISTS OF EDINBURGH.—At Royal Faculty of Physicians and Surgeons, 5.15 p.m., combined meeting with Glasgow and West of Scotland Society. Mr. E. Brewin: Acid Base Balance.
BRITISH ASSOCIATION OF SPORT AND MEDICINE.—At London School of Hygiene and Tropical Medicine, 10 a.m., joint lecture meeting with Ergonomics Research Society.
CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Chest Clinic, Castle Hill, Cambridge, symposium on Respiratory Diseases. *Morning:* 10.30 a.m., Dr. R. A. Bruce: Pulmonary Manifestations of Sarcoidosis; 11.30 a.m., Dr. M. J. Greenberg: Place of B.C.G. Vaccination; 12.15 p.m., Dr. E. M. Cheffins: Pulmonary Complications of General Disease. *Afternoon:* 2.30 p.m., Mr. C. Parish: Clinical Presentation of Carcinoma of the Bronchus; 3.15 p.m., Dr. P. K. M. Barrett: Drug Treatment of Pulmonary Tuberculosis; 4 p.m., Any Questions?

Sunday, October 29

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., seminar. Mr. S. E. Birdsall: Common Ear, Nose, and Throat Conditions.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Llewelyn.—On September 14, 1961, to Dr. Joan (formerly Macdonald), wife of David A. B. Llewelyn, of Little Oaks, Park View Road, Woldingham, Surrey, a son.

DEATHS

Low.—On September 26, 1961, at 16 Jubilee Grove, Lymm, Cheshire, Monica Low, M.R.C.S., L.R.C.P., D.O.M.S., late of Blackpool, Lancs, aged 57.
Macrae.—On September 19, 1961, at Salisbury, Southern Rhodesia, Archibald Campbell Macrae, M.B., Ch.B., Colonel, I.M.S., retired, of Mount Charles, Moffat, Dumfriesshire.
McGowan.—On September 22, 1961, at Woodend Hospital, Aberdeen, John Pool McGowan, M.D., M.R.C.P.Ed., D.T.M.&H., of 16 Ruthrichill Road, Stoneywood, Aberdeen.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Dextro-thyroxine and Hypercholesterolaemia

Q.—*What is the value of dextro-thyroxine in hypercholesterolaemia?*

A.—It has been known for many years that patients with hypothyroidism frequently have a raised level of serum cholesterol and that when they are treated with active thyroid preparations the serum cholesterol level returns towards normal. It was natural, therefore, that the effect of thyroid preparations should be tried in other conditions with hypercholesterolaemia. It was soon found that, although some reduction in the level of serum cholesterol could be obtained, this form of treatment was impracticable because symptoms of hyperthyroidism developed and frequently angina of effort was either provoked or aggravated. Within recent years a number of compounds analogous to the metabolically active thyroid hormones have been developed, and it was naturally hoped that one of these might retain the cholesterol-lowering properties without having the metabolic activity. Of these preparations the most promising appears to be D-thyroxine.

Greene and Farran[1] found that D-thyroxine had only about one-tenth of the metabolic activity of L-thyroxine. D-Thyroxine has been used both in this country and in America as an agent for lowering serum cholesterol, and present evidence both from animal experiments[2] and from clinical studies[3 4] suggests that it can do so without increasing the basal metabolic rate (B.M.R.). Boyd and Oliver[3] gave D-thyroxine to 36 euthyroid patients in doses ranging from 10 to 60 mg. daily. All patients showed a lowering of serum cholesterol, but only 6 patients, 3 of them on high doses, had an increase in B.M.R. Starr and his colleagues[4] treated 43 patients with hypercholesterolaemia due to various causes. They gave doses of 2 to 16 mg. of D-thyroxine for periods of one to eighteen months, and obtained a significant and sustained reduction in serum cholesterol in all but one of these. They did not observe any toxic effects, and commented that D-thyroxine has little calorigenic potency but has stronger cholesterol-lowering properties than L-thyroxine. In a more recent paper Oliver and Boyd[5] report on the use of D-thyroxine in 38 euthyroid patients with ischaemic heart disease, all of whom had a raised serum cholesterol. The majority of these patients had a significant and sustained fall in their serum cholesterol with a dose of 7.5 to 10 mg. Six, however, did not respond, and in 5 patients the serum cholesterol level rose after six months although they were still on D-thyroxine. Three patients (2 on the 10 mg. dose and 1 on the 7.5 mg. dose) developed angina during treatment, and 7 others with angina had less angina, and their exercise tolerance improved when treatment with D-thyroxine was stopped. Oliver and Boyd comment, "Although our previous investigations have indicated that D-thyroxine is at present the most satisfactory thyro-active compound for reduction of hypercholesterolaemia in patients with coronary heart disease, it is not good enough."

In summary, therefore, there is good evidence that D-thyroxine will lower the raised serum cholesterol in the majority of euthyroid hypercholesterolaemic patients but it may provoke or aggravate cardiac symptoms, and there is to date no evidence that such treatment influences the clinical course of atherosclerosis.

References

1 Greene, R., and Farran, H. E. A., *Brit. med. J.*, 1958, 2, 1057.
2 Boyd, G. S., and Oliver, M. F., *J. Endocr.*, 1960, 21, 25.
3 —— —— ibid., 1960, 21, 33.
4 Starr, P., Roen, P., Freibrun, J. L., and Schleissner, L. A., *Arch. intern. Med. (Chicago)*, 1960, 105, 830.
5 Oliver, M. F., and Boyd, G. S., *Lancet*, 1961, 1, 783.

Progesterone Deficiency and Abortion

Q.—*Is progesterone likely to be of value in a young woman in whom two pregnancies have terminated at about 8 weeks and who is very keen to have a child?*

A.—Abortion at 2 months is most often due to some fault in the development of the fertilized egg, but gross general disease (e.g., diabetes) and local abnormality (e.g., congenital uterine malformation) should be excluded. Progesterone deficiency has not been shown to be an important causal factor, and progesterone therapy is rational only if the continuation of pregnancy is threatened by such a deficiency. Unfortunately there is no practical and consistently reliable method of determining the presence of progesterone deficiency, so we have to use the level of urinary pregnanediol, a metabolite of progesterone. This level might be assayed weekly for the first 14 weeks of this patient's next pregnancy, and if the level is subnormal one of the oral synthetic progestogens can be prescribed.

Embalming

Q.—*What immediate treatment should be given to preserve a body in the tropics? Should the arterial blood be replaced by formalin, and, if so, what is the technique?*

A.—Embalming is a specialized and sometimes complicated procedure, of which a full account is given in *The Disposal of the Dead*.[1] The techniques are directed not only to the prevention of decomposition but also to achieving a natural cosmetic effect. If, however, the sole consideration is the retarding of putrefaction, the treatment is not difficult provided the body can be injected within a few hours after death, before the blood loses its fluidity.

An axillary artery and vein are first exposed. The vein is ligated and a wide-bore tube tied into the proximal part; this is for drainage of the blood, and, since this must be intermittent, some form of clamp must be provided. At the outset the vein tube is kept closed. The artery is opened and a rubber tube tied into the distal part, through which 2–3 pints (1.1–1.7 litres) of 1–2% formaldehyde can be injected into the arm by the careful use of a Higginson's syringe or by gravity from a gallon (4.5 litres) container placed 5 ft. (1.5 m.) above the body. The lower part of the artery is then ligated and the artery tube tied into the proximal part so that the rest of the body can be injected. As 1–2 pints (0.6–1.1 litres) of 1–2% formaldehyde are run in the veins of each temple distend, the hypostasis begins to clear, and the facial tissues fill out. When 0.5–1 gallon (2.3–4.5 litres) of the solution has been used the venous system will be engorged and can be drained by releasing the clamp on the vein tube. Until mixed with embalming fluid the blood which flows is thick, and drainage is aided by manipulation of the tube, cleaning it with a plunger, and by raising the limbs and massaging towards the trunk. When the flow of blood decreases the vein tube is again clamped and more formaldehyde solution is injected into the artery. The pressure which is re-established in the veins has an important function in assisting diffusion of the fluid into the tissues and preventing the embalming fluid from by-passing the capillary bed. After the injection of each 2–3 pints the vein is drained and gradually the returned fluid becomes thinner as the blood is mixed with the formaldehyde solution. The total number of pints of 2% formaldehyde solution sufficient for treatment is one more than the weight of the body in stones (1 stone = 6.4 kg.). Some prefer to use twice the volume of a 1% solution.

Attention is then turned to the viscera, which are not usually adequately treated by arterial injection alone. A small incision is made in the upper abdomen to enable a pointed metal tube 12 in. (30.4 cm.) long and of at least ¼ in. (6.4 mm.) internal diameter to be inserted into the trunk. This tube is connected to an aspirating jar, and by its manipulation the heart, lungs, and hollow viscera can be punctured and the released fluids sucked out. Then

before the tube is withdrawn it is used to distribute 1–3 pints (0.6–1.7 litres) of 15% formaldehyde solution throughout the trunk cavities. The skin wound is closed by a purse-string suture.

The body is then arranged in the required posture and examined after a few hours for adequacy of fixation as judged by the firmness of the tissues. Areas which still feel soft have not been reached by the embalming fluid and must be injected locally with 2% formaldehyde solution from a 20-ml. syringe fitted with an intramuscular needle.

REFERENCE

[1] Polson, C. J., Brittain, R. P., and Marshall, T. K., *The Disposal of the Dead*, 1953. English Universities Press, London.

Examinations for Life Assurance

Q.—*Why do insurance companies ask candidates for life assurance such outmoded questions as: "Have you ever spat blood?"; "Is there any insanity in your family?"; or "Have you had syphilis?", yet not request such simple things as a haemoglobin estimation, a blood W.R., or an x-ray examination of the chest?*

A.—The premise that the questions referred to are outmoded cannot be accepted. They are part of the normal process of history-taking which is showing sad signs of becoming a lost art and a neglected activity. Some forms of mental disease have a strong hereditary pattern.

Underwriters and chief medical officers, like good examiners, do not in most instances arrive at diagnoses solely upon the answers to the questions in the examination forms. The questions, even the "outmoded" ones, are intended to serve as jumping-off points for the examiner to reach a reasoned conclusion as to *life expectancy*, not, as seems too often to be the examiner's aim, as to the proposer's *current condition*. The answers to the questions mentioned, like others, also provide evidence as to the character of the proposer, and, when taken together with information supplied by the private medical attendant or hospital or clinic attended, as to his veracity. Non-disclosure is a cardinal sin in underwriter's eyes.

The practising clinician knows that the tests listed by the questioner must be used in conjunction with the rest of the clinical findings and are not themselves the be-all and end-all of medical diagnosis. The estimation of haemoglobin, except in the hands of experts, is notoriously unreliable. The blood Wassermann reaction (W.R.) is associated in routine use with a false-negative rate varying from about 2–5% in the primary and secondary stages to as much as 50% in the latent stage of neurosyphilis, and much the same can be said of the Kahn and similar tests. The false-negative rate varies as between laboratories. Reliance upon a single routine W.R. for the conclusion of a financial contract would therefore be very unwise.

Haemoptysis may be a lead to conditions other than pulmonary tuberculosis and cancer of the lung—for instance, the bleeding bronchiectatic cavity with little fibrosis to ensure a definite diagnosis on straight *x*-ray examination of the chest—while mitral stenosis with haemoptysis may not be conclusively shown in a single *x*-ray plate, requiring instead or as well a careful history and thorough physical examination.

Life officers, whose object is to write as much business as possible and to do so in a businesslike way, have found increasing resistance by bona-fide proposers even to ordinary medical examination. The more extra requirements the greater the resistance and the greater the expense to proposer or company. Proposers living in remote places would refuse to attend at distant laboratories or *x*-ray departments. Factors of this kind have caused a great increase in the amount of non-medical business written by the life offices.

In spite of the inference which might be drawn from the question underwriting is a more exact science than medical diagnosis and prognosis, on the maximum attainable exactness of which, however, it obviously must depend.

Portable Oxygen Apparatus

Q.—*A patient with cor pulmonale and chronic bronchitis has been issued by a hospital with a portable oxygen apparatus. This has given a new lease of activity to a man who is dyspnoeic even after talking. Are these machines now generally available, and in what conditions would their use be indicated?*

A.—The apparatus for portable oxygen was described by Cotes and Gilson.[1] It is generally available but is not prescribable under the N.H.S. The oxygen may be prescribed but not the apparatus. In general it is suitable for people who show severe breathlessness with desaturation on exercise. The best test of suitability is to get the patient to walk 50 yards with and without oxygen and to see whether his distress is relieved. If he is as breathless with oxygen as he was without then it is no good to him, but if it relieves his dyspnoea it is worth a trial.

REFERENCE

[1] Cotes, J. E., and Gilson, J. C., *Lancet*, 1956, **1**, 872.

Tropical Eosinophilia and Parasitic Infections

Q.—*Is there any known relationship between tropical eosinophilia and microfilaria? What is the best and cheapest form of treatment for the former?*

A.—There is now a good deal of evidence indicating that so-called tropical eosinophilia often results from the invasive stage of human or animal filarial or intestinal helminthic infections. Wherever possible such cases should be fully investigated and if necessary followed for a period of three to six months, for it may not be possible to find microfilariae or eggs of the causal parasite until such an interval has passed. Treatment depends on the cause, but if evidence of a filarial basis for the condition is found the standard course of diethylcarbamazine is the most satisfactory form of treatment.

NOTES AND COMMENTS

Antimisters for Spectacles.—Dr. M. W. Paterson (Glasgow W.2) writes: Should the elegant solutions recommended in your issue of September 23 ("Any Questions? p. 841) not be to hand one may moisten finger and thumb on a damp cake of soap, smear a thin film over both sides of each lens, and polish off lightly. This is cheap and effective.

Our Expert replies: I have tried the method suggested by Dr. Paterson and it works quite well, although not giving quite such a bright, clear appearance to the spectacles as the antimist solutions.

Correction.—In the Medical Memorandum on "Home-made Wine as a Cause of Lead-poisoning" (October 7, page 939) we regret omitting quotation marks round calcium disodium "versenate," which is a proprietary brand of sodium calciumedetate.

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